

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 021998/S-002

Trade Name: **Plan B One-Step**

Generic Name: **Levonorgestrel**

Sponsor: **Teva Branded Pharmaceutical Products R&D, Inc.**

Approval Date: **04/30/2013**

Indications: This “Prior Approval” supplemental new drug application provides for making Plan B One-Step available over the counter to women of childbearing potential aged 15 years and over who are in need of emergency contraception.

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APPLICATION NUMBER:
NDA 021998/S-002

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APPLICATION NUMBER:
NDA 021998/S-002

APPROVAL LETTER



NDA 021998/S-002

SUPPLEMENT APPROVAL

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: Amy Hummel, M.S.
Associate Director, Regulatory Affairs
41 Moores Road, P.O. Box 4011
Frazer, PA 19355

Dear Ms. Hummel:

Please refer to your supplemental new drug application dated and received February 7, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B One-Step® (levonorgestrel) tablet, 1.5 mg.

We also refer to your submissions dated March 9, 2012, June 11, 2012, June 27, 2012, March 13, 2013, April 4, 2013, and April 15, 2013. The March 9, 2012, submission constituted a complete response to our December 7, 2011 action letter. This "Prior Approval" supplemental new drug application provides for making Plan B One-Step available over the counter to women of childbearing potential aged 15 years and over who are in need of emergency contraception.

We note that the approved labeling contains the language "not for sale to those under 15 years of age * proof of age required * not for sale where age cannot be verified." Therefore, you must have appropriate mechanisms in place to ensure that the age of the purchaser is verified at the point of purchase.

We also note and agree with your plan to audit retail outlets, described in your submission dated March 13, 2013, that is designed to assure consumer compliance with the approved labeling. We request that you submit a report of your findings for review by the agency upon completion.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

LABELING

Submit final printed labeling, as soon as it is available, but no more than 30 days after it is printed. The final printed labeling (FPL) must be identical to the enclosed labeling:

- immediate container labels (1-count blister) submitted on October 21, 2011,
- clinic and retail outer carton labels submitted on April 15, 2013,
- clamshell label front and back cards (Product identification cards) submitted on April 15, 2013, and
- consumer information leaflet submitted on December 7, 2011

and must be in the “Drug Facts” format (21 CFR 201.66), where applicable.

The final printed labeling should be submitted electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Labeling for approved NDA 021998/S-002.**” Approval of this submission by FDA is not required before the labeling is used.

DRUG REGISTRATION AND LISTING

All drug establishment registration and drug listing information is to be submitted to FDA electronically, via the FDA automated system for processing structured product labeling (SPL) files (eLIST). At the time that you submit your final printed labeling (FPL), the content of labeling (Drug Facts) should be submitted in SPL format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>. In addition, representative container or carton labeling, whichever includes Drug Facts, (where differences exist only in the quantity of contents statement) should be submitted as a JPG file.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Doris J. Bates, Ph.D., Senior Regulatory Project Manager, at (301) 796-1040.

Sincerely,

{See appended electronic signature page}

Shaw T. Chen, M.D., Ph.D.,
Director (Acting)
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE(S):

Carton and Container Labeling
Product Identification Cards
Consumer Information Leaflet

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/s/

SHAW T CHEN
04/30/2013

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:
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OTHER ACTION LETTERS



NDA 021998/S-002

COMPLETE RESPONSE

Teva Women's Health, Inc.
Attention: Valerie M. Mulligan
Senior Director, Regulatory Affairs
425 Privet Road
P.O. Box 1005
Horsham, PA 19044

Dear Ms. Mulligan:

Please refer to your Supplemental New Drug Application (sNDA) dated February 7, 2011, received February 7, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B[®] One-Step (levonorgestrel) tablets, 1.5 mg.

We acknowledge receipt of your submissions dated March 31, April 4, and April 6, May 18, June 1, June 3, June 21, July 25, September 28, October 21, October 25, November 4, November 15, and December 7, 2011.

This "Prior Approval" supplemental new drug application proposes to expand the existing nonprescription patient population to allow for the nonprescription availability of Plan B[®] One-Step for all women of child-bearing potential.

We have completed our review of this application, as amended. As reflected in the reviews for this application, the Division was prepared to approve the application. In preparation for the action date the Commissioner reviewed and considered data, information, and analysis provided to her by CDER. She concluded that CDER had identified reasonable scientific bases for its scientific determination that levonorgestrol 1.5 mg tablet (Plan B One-Step) is safe and effective for non-prescription use to reduce the chance of pregnancy after unprotected sex for all women of child-bearing potential.

This morning, FDA received from the Secretary of Health and Human Services the attached Memorandum stating that the Secretary has reached a different conclusion regarding the adequacy of the data in your supplement to support approval. Referring to her authority under the Federal, Food, Drug, and Cosmetic Act, the Secretary has directed me to issue a complete response letter because she believes the data "submitted for this product are inadequate to support approval in that they do not establish that prescription dispensing requirements should be eliminated for all ages."

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your

lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

If you have any questions, call Melissa Hancock Furness, Supervisory Regulatory Project Manager, at (301) 796-0893.

Sincerely,

{See appended electronic signature page}

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration


Attached



THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

MEMORANDUM

TO: Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

FROM: Kathleen Sebelius 

SUBJECT: Supplemental New Drug Application (NDA 21-998/S002)

DATE: December 7, 2011

On February 7, 2011, Teva Women's Health Inc. submitted to the Food and Drug Administration (FDA) a supplemental new drug application (NDA 21-998/S002) for Plan B One-Step (levonorgestrel 1.5 mg), an emergency contraceptive that can prevent pregnancy if taken within 72 hours of sexual intercourse. The application seeks FDA approval to market Plan B One-Step as a non-prescription drug product without any age restriction. Currently, this drug product, like other FDA-approved (levonorgestrel) emergency contraception drug products, is sold exclusively from behind the pharmacy counter and is available without a prescription only for women ages 17 years and older; women 16 and younger can obtain this drug product only by prescription.

I have carefully considered FDA's Division Director Summary Review of Regulatory Action, dated November 30, 2011, for the supplemental application, which represents the position of the FDA and recommended approval of the application. Based on my review, I have concluded that the data submitted for this product do not establish that prescription dispensing requirements should be eliminated for all ages.¹

The label comprehension and actual use studies submitted to FDA do not include data on all ages for which the drug would be approved and available over-the-counter. Yet, it is commonly understood that there are significant cognitive and behavioral differences between older adolescent girls and the youngest girls of reproductive age, which I believe are relevant to making this determination as to non-prescription availability of this product for all ages. Although the average age of the onset of menses for girls in the United States is 12.4 years of age, about ten percent of girls reach menarche by 11.1 years of age.² If the application is approved, the product would be available, without a prescription or other point-of-sale restrictions, even to the youngest girls of reproductive age.

¹ See 21 C.F.R. § 310.200(b).

² Chumlea WC, Schubert CM, Roche AF, Kulin HE, Lee PA, Himes JH, Sun SS: Age at Menarche and Racial Comparisons in U.S. Girls. *Pediatrics* 2003;111(1): 110-113.

The Federal Food, Drug, and Cosmetic Act provides that “[t]he Secretary [of Health and Human Services], through the Commissioner, shall be responsible for executing” its provisions.³ As such, I direct FDA to issue a complete response letter because the data submitted for this product are inadequate to support approval in that they do not establish that prescription dispensing requirements should be eliminated for all ages.

³ 21 U.S.C. § 393(d)(2).

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/s/

JANET WOODCOCK
12/07/2011

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LABELING





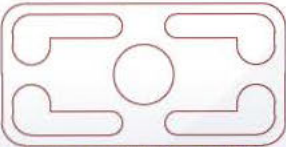
799-30-100583 Iss. 4/2013

PlanB One Step
emergency contraceptive

PlanB One Step
emergency contraceptive
One Tablet. One Step.



PlanB One Step
emergency contraceptive
One Tablet. One Step.



- The sooner you take it, the more effective it will be
- Take as soon as possible within 72 hours (3 days) after unprotected sex
- Will not harm an existing pregnancy



PlanB One Step

emergency contraceptive

One Tablet. One Step.

The sooner you take it, the more effective it will be

Take as soon as possible within 72 hours (3 days) after unprotected sex

Will not harm an existing pregnancy

- not for sale to those under 15 years of age
- proof of age required
- not for sale where age cannot be verified

Visit us at:
www.PlanBOneStep.com

Drug Facts	Purpose	
Active ingredient Levonorgestrel 1.5mg	Emergency contraceptive	
Use: For women to reduce chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)		
Warnings		
Allergy alert: Do not use if you have ever had an allergic reaction to levonorgestrel		
Sexually transmitted disease (STDs) alert: This product does not protect against HIV/AIDS or other STDs		
Do not use:		
• if you are already pregnant (because it will not work) after regular birth control		
When using this product you may have:		
• menstrual changes	• dizziness	• breast pain
• nausea	• headache	• vomiting
• lower stomach (abdominal) pain	• dizziness	
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control center right away.		
Directions		
• women 15 years of age and older: take as soon as possible within 72 hours (3 days) after unprotected sex. The sooner you take it the better it will work.		
• women under 15 years of age: talk to a doctor		
• if you vomit within 2 hours after taking the medication, call a healthcare professional to find out if you should repeat the dose		
Other information		
• Read the instructions, warnings and enclosed product insert before use		
• This product works mainly by preventing ovulation (egg release). It may also prevent fertilization of a released egg (sperm and egg) or attachment of a fertilized egg to the uterus (implantation).		
• Do not use if certain to open or your strip is removed or blister seal is broken or missing		
• Store at 20-25°C (68-77°F)		
Inactive ingredients		
• Ethanol, croscarmellose sodium, starch, lactose monohydrate, magnesium stearate, polyethylene glycol		
Questions?		
Call 1-800-448-1271 or visit www.PlanBOneStep.com		

FOR CLINIC USE ONLY. NOT FOR RESALE.

For age 15 and older

NDC 51285-964-19

PlanB One Step
levonorgestrel 1.5 mg

emergency contraceptive

Reduces chance of pregnancy after unprotected sex.
Not for regular birth control.

One Tablet. One Step.

Contains 1 Tablet 1.5mg



TEVA

TEAR HERE TO OPEN



798-30-100582 Iss. 4/2013

PlanB One-Step emergency contraceptive
One Tablet, One Step.

PlanB One-Step emergency contraceptive

One Tablet, One Step.

The sooner you take it, the more effective it will be

Take as soon as possible within 72 hours (3 days) after unprotected sex

Will not harm an existing pregnancy

- not for sale to those under 15 years of age
- proof of age required
- not for sale where age cannot be verified

Visit us at: www.PlanBOneStep.com

Drug Facts

Active Ingredient Levonorgestrel (Ling)	Purpose Emergency contraceptive
---	---

Use For women to reduce chance of pregnancy after unprotected sex (if a contraceptive tablet or if you did not use birth control)

Warnings
Allergy alert: Do not use if you have ever had an allergic reaction to levonorgestrel

Seriously transmitted diseases (STDs) alert: This product does not protect against HIV/AIDS or other STDs.

Do not use
 • If you are already pregnant (because it will not work)
 • For regular birth control

When using this product you may have
 • menstrual changes • breast pain
 • nausea • headache • vomiting
 • lower stomach (abdominal) pain • dizziness

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control center right away.

Directions
 • Women 15 years of age and older: take as soon as possible within 72 hours (3 days) after unprotected sex. The sooner you take it the better it will work.
 • Women under 15 years of age: talk to a doctor.
 • If you vomit within 2 hours after taking the medication, call a healthcare professional to find out if you should repeat the dose.

Other Information
 • Read the instructions, warnings and enclosed product insert before use.
 • This product works mainly by preventing ovulation (egg release). It may also prevent fertilization of a released egg (joining of sperm and egg) or attachment of a fertilized egg to the uterus (implantation).
 • Do not use if caplet is open or has chips or holes and is broken or missing.
 • Store at 25-30°C (77°F).

Inactive Ingredients
 • lactose • croscarmellose sodium • croscarmellose sodium • croscarmellose sodium • croscarmellose sodium • croscarmellose sodium

Questions?
 Call 1-800-428-1271 or visit www.PlanBOneStep.com

For age 15 and older NDC 51285-943-88

PlanB One-Step emergency contraceptive
One Tablet, One Step.

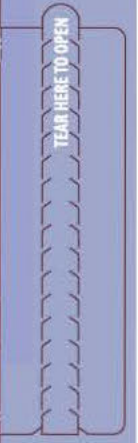
PlanB One-Step levonorgestrel 1.5 mg

emergency contraceptive

Reduces chance of pregnancy after unprotected sex. Not for regular birth control.

One Tablet, One Step.

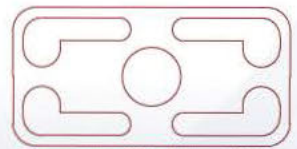
Contains 1 Tablet 1.5mg



PlanB One-Step emergency contraceptive
One Tablet, One Step.



PlanB One-Step emergency contraceptive
One Tablet, One Step.



- The sooner you take it, the more effective it will be
- Take as soon as possible within 72 hours (3 days) after unprotected sex
- Will not harm an existing pregnancy

PlanB One-Step

1 Tablet (Levonorgestrel) 1.5mg



TEVA

The logo features a stylized green and blue wave or 'C' shape above the text.

Plan B
One-Step®

NEW!

***Now Available
Over the Counter***

The logo for Plan B One-Step features a stylized, overlapping shape in shades of green and blue, resembling a partial circle or a protective shield, positioned above the product name.

Plan B
One-Step®

*Reduces chance
of pregnancy after
unprotected sex.*

What is Plan B One-Step®?

Plan B One-Step® is emergency contraception that helps prevent pregnancy after birth control failure or unprotected sex. It is a **backup** method of preventing pregnancy and should not be used as regular birth control.

What Plan B One-Step® is not.

Plan B One-Step® will not work if you are already pregnant and will not affect an existing pregnancy. Plan B One-Step® will not protect you from HIV Infection (the virus that causes AIDS) and other sexually transmitted diseases (STDs).

When should I use Plan B One-Step®?

The sooner you take emergency contraception, the better it works. You should use Plan B One-Step® within 72 hours (3 days) **after you have had unprotected sex.**

Plan B One-Step® is a backup or emergency method of birth control you can use when:

- your regular birth control was used incorrectly or failed
- you did not use any birth control method

When not to use Plan B One-Step®.

- Plan B One-Step® should not be used:
- as a regular birth control method, because it's not as effective as regular birth control.
 - if you are already pregnant, because it will not work.
 - if you are allergic to levonorgestrel or any other ingredients in Plan B One-Step®.

How does Plan B One-Step® work?

Plan B One-Step® is one tablet with levonorgestrel, a hormone that has been used in many birth control pills for several decades. Plan B One-Step® contains a higher dose of levonorgestrel than birth control pills, but works in a similar way to prevent pregnancy. It works mainly by stopping the release of an egg from the ovary. It is possible that Plan B One-Step® may also work by preventing fertilization of an egg (the uniting of sperm with the egg) or by preventing attachment (implantation) to the uterus (womb).

How can I get the best results from Plan B One-Step®?

You have 72 hours (3 days) to try to prevent pregnancy after birth control failure or unprotected sex. **The sooner you take Plan B One-Step®, the better it works.**

How effective is Plan B One-Step®?

If Plan B One-Step® is taken as directed, it can significantly decrease the chance that you will get pregnant. About 7 out of every 8 women who would have gotten pregnant will not become pregnant.

How will I know Plan B One-Step® worked?

You will know Plan B One-Step® has been effective when you get your next period, which should come at the expected time, or within a week of the expected time. If your period is delayed beyond 1 week, it is possible you may be pregnant. You should get a pregnancy test and follow up with your healthcare professional.

Will I experience any side effects?

- some women may have changes in their period, such as a period that is heavier or lighter or a period that is early or late. **If your period is more than a week late, you may be pregnant.**
- If you have severe abdominal pain, you may have an ectopic pregnancy, and should get immediate medical attention.
- when used as directed, Plan B One-Step® is safe and effective. Side effects may include changes in your period, nausea, lower stomach (abdominal) pain, tiredness, headache, dizziness, and breast tenderness.
- If you vomit within 2 hours of taking the medication, call a healthcare professional to find out if you should repeat the dose.

What if I still have questions about Plan B One-Step®?

If you have questions or need more information, call our toll-free number, 1-800-330-1271, or visit our website at www.PlanBOneStep.com.

Other Information

Keep out of reach of children:

In case of overdose, get medical help or contact a Poison Control Center right away at 1-800-222-1222.

Do not use if the blister seal is opened.

Store at room temperature 20–25°C (68–77°F).

Active Ingredient: levonorgestrel 1.5 mg

Inactive Ingredients: colloidal silicon dioxide, potato starch, magnesium stearate, talc, corn starch, lactose monohydrate

1-800-330-1271

www.PlanBOneStep.com



799-33-100269



If you are sexually active, you should see a healthcare provider for routine checkups. Your healthcare provider will talk to you about and, if necessary, test you for sexually transmitted diseases, teach you about effective methods of routine birth control and answer any other questions you may have.

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/s/

SHAW T CHEN
04/30/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021998/S-002

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	November 30, 2011
From	Andrea Leonard-Segal, M.D., M.S.
Subject	Division Director Summary Review
NDA/BLA #	21-998/S002
Supplement #	
Applicant Name	Teva Women's Health, Inc.
Date of Submission	February 7, 2011
PDUFA Goal Date	December 7, 2011
Proprietary Name / Established (USAN) Name	Plan B® One-Step / levonorgestrel
Dosage Forms / Strength	Tablet / 1.5 mg
Proposed Indication(s)	Reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Christina Chang, M.D., 10/5/2011
Statistical Review	Rima Izem, Ph.D., 10/12/2011
Social Scientist Review Plan B® One-Step	Oluwamurewa, Oguntimein, M.S., 07/25/2011
Social Scientist Review Plan B®	Karen Lechter, J.D., Ph.D. 11/05/03
OSI Review	Sharon K. Gershon, Pharm.D., 09/23/2011
Labeling Reviews	Maria Ysern, M.Sc., Colleen Rodgers, Ph.D., 09/29/11, 10/27/11 and 11/16/11
CDTL Review for NDA 21-998/S002	Lesley-Anne Furlong, M.D., 10/25/2011
CDTL Review for NDA 21-998	Lisa M. Soule, M.D. 07/09/2009
OSE Reviews	1. Mark Miller, Pharm D., Adrienne Rothstein, Pharm D., Linda Scarazzini, M.D., 11/10/11 2. Teresa Rubio, Daniel Davis, M.D., Audrey Gassman, Robert Boucher, M.D. 915 review 06/13/2011 3. Mark Miller, Pharm.D., Melissa Truffa R. Ph., Robert Boucher, M.D., Gerald Dal Pan, M.D., 06/19/09 Plan B® (levonorgestrel), NDA 21-045. 4. Adrienne Rothstein, Pharm D. and Melissa Truffa R.Ph., 04/07/08 NDA 21-045.
Pediatric and Maternal Health Staff Consult	Lisa Mathis, M.D., 10/11/2011

OND=Office of New Drugs
 DDMAC=Division of Drug Marketing, Advertising and Communication
 OSE= Office of Surveillance and Epidemiology
 OSI=Office of Scientific Investigations
 CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

On February 7, 2011, Teva Women's Health, Inc. (Teva) submitted an efficacy supplement to NDA 21-998 that provides data intended to support the marketing of Plan B® One-Step (levonorgestrel 1.5 mg) as a nonprescription product to all women of reproductive potential without an age restriction. Plan B® One-Step has been found to be a safe and effective emergency contraceptive (EC) for all women of reproductive age. Currently, Plan B® One-Step is available as a nonprescription product for women ages 17 years and older. The younger population in need of ECs must obtain a prescription before they can purchase the medication. The different marketing status for these different age groups reflects the complicated regulatory history of levonorgestrel as an emergency contraceptive.

To support this efficacy supplement Teva has submitted the following information:

- Label Comprehension Study (Study DR-LEV-301)
- Actual Use Study (Study DR-LEV-301)
- Literature Review
- Analysis of Postmarketing Safety Data
 - Teva's postmarketing database
 - FDA's Adverse Event Reporting System (AERS)
 - World Health Organization's International Drug Monitoring Program (WHO)
 - Drug Abuse Warning Network (DAWN)
 - American Association of Poison Control Centers data (AAPCC)
 - 120-Day Safety Update
- Proposed Labeling

This review will address the new efficacy supplement in the context of the regulatory history of Plan B® and Plan B® One-Step.

2. Background

Levonorgestrel is a second generation progestin derived from norgestrel. It has been available in hormonal contraceptive products for decades. Among the approved levonorgestrel-containing products are Plan B®, levonorgestrel 0.75 mg, and Plan B® One-Step, levonorgestrel 1.5 mg. Both of these are orally administered ECs and tens of millions of the products have been sold in the United States since they were approved. Data from Teva indicates that from July 2009 (when Plan B® One-Step was approved) through January 2011 a total of (b) (4) units of Plan B® were distributed and, excluding non-profit clinics, (b) (4) units were distributed commercially. Of these, 19.5% of prescriptions were for patients 16 years of age and younger. (These data do not account for generic sales of levonorgestrel EC.) For Plan B® One-Step, (b) (4) units were distributed by Teva of which (b) (4) were

commercially distributed units (71%). Prescriptions for patients 16 years of age and younger accounted for 6.4% of the commercially distributed units.

The exact mechanism of action for levonorgestrel as an emergency contraceptive is not known. Levonorgestrel is thought to act by delaying ovulation post-coitally by impairing follicular maturation and disrupting mechanisms involved in the luteinizing hormone surge. Postovulatory mechanisms of action may include such things as interference with fertilization resulting from changes in cervical mucus and uterine fluid that impede sperm penetration and migration. The effect of Plan B One-Step, if any, on implantation of a fertilized egg is unknown. There is no medical evidence that levonorgestrel can impact the course of a pregnancy once implantation has occurred; there is no medical evidence that Plan B® One-Step or Plan B® would harm a developing baby.

Plan B® was initially approved in the United States as a prescription-only EC on July 28, 1999. The treatment regimen for Plan B® consists of two doses; the first 0.75 mg tablet is to be taken as soon as possible within 72 hours of having unprotected sexual intercourse or a known or suspected contraceptive failure and the second tablet is to be taken 12 hours later. This product was approved for over-the-counter (OTC) marketing for women ages 18 and older on August 24, 2006 via NDA 21-045/S-011. It remained a prescription (Rx) product for females 17 years of age and younger. At the time of the partial OTC switch, Plan B® was approved as a single package configuration for dual prescription and nonprescription (OTC) marketing. Since the carton bore the statement “Rx only for age 17 and younger,” the product was required to be kept behind the pharmacy counter and/or distributed by licensed practitioners. The Plan B® OTC population was expanded to include 17-year-old women in 2009 under an efficacy supplement. This occurred on the same day that NDA 21-998 for Plan B® One-Step (a single levonorgestrel 1.5 mg tablet dosing regimen) was approved OTC for women ages 17 and older and by prescription for those less than 17 years of age. A single package configuration for dual prescription and OTC marketing was then the situation for both Plan B® and for Plan B® One-Step.

The regulatory histories of the OTC approvals for Plan B® (NDA 21-045) and Plan B® One-Step (NDA 21-998) have been interwoven and complex. Several sponsors/applicants have been involved along the way as ownership of the products has changed hands (Women’s Capital Corporation, Barr Research, Inc, Duramed Pharmaceuticals, Inc., Teva Women’s Health, Inc.). In her review, Dr. Christina Chang has nicely distilled the regulatory history as it applies to this Plan B® One-Step efficacy supplement. I will highlight certain parts of the regulatory history here.

In April 2003 Barr Research, Inc. (Barr) submitted a supplement to NDA 21-045 to switch Plan B® (levonorgestrel 0.75 mg) OTC for all women of reproductive age. In 2004, this application was presented at a joint meeting of the Nonprescription Drug Advisory Committee and the Advisory Committee for Reproductive Health Drugs. The committee recommended that the NDA supplement should be approved OTC for all ages (by a vote of 23 to 4). So did all of the FDA primary and secondary review staff (with the exception of one medical officer in the Division of Over-the-Counter Drug Products), the Deputy Directors of the involved FDA divisions, Drs. Rosebraugh and Griebel (who had been delegated responsibility for the

application) and the directors of the Offices involved in the application (Drs. Jonca Bull, Florence Houn, and John Jenkins). Dr. Stephen Galson, then the acting director of the Center for Drug Evaluation Research (CDER), disagreed with the recommendations for approval and in May, 2004 issued a Not Approvable letter because of the “lack of available data relevant to OTC use of the product by adolescents younger than 14 and very limited data in the 14 – 16 age group.”

Two months later, the applicant submitted a Complete Response to the Not Approvable letter in which they proposed to switch Plan B® to OTC status for women 16 years of age and older. In an August 26, 2005 memorandum, Dr. Steven Galson, Director, CDER, concluded that the label comprehension and actual use data submitted with the application supported OTC use of Plan B® by women aged 17 years and older, but not by females ages 16 years and younger. Additional data would be needed in the younger population. On the same date, Commissioner Crawford signed a letter telling the applicant (at this point, Duramed Pharmaceuticals, Inc. (Duramed)) that their product could not be legally marketed OTC in the United States and that FDA had decided to publish an advance notice of proposed rulemaking asking for public comments on when an active ingredient can be simultaneously marketed in both a prescription and an OTC drug product and also on questions related to the marketing of Rx and OTC versions of the same active ingredient in a single package.

In a letter dated July 31, 2006, Dr. Andrew von Eschenbach, then Acting Commissioner of FDA, informed the sponsor that the Agency had determined that “it is not necessary to engage in rulemaking to resolve the novel regulatory issues raised by your application.” Dr. von Eschenbach further indicated that the Agency would like to meet with Duramed to discuss resumption of review of their sNDA for the Rx to OTC switch of Plan B® for emergency contraception in women 18 years of age and older.

Duramed subsequently met with the Agency on August 8, 2006. During that meeting issues related to the age cutoff for OTC marketing and the sponsor’s proposed Convenient Access, Responsible Education Program (CARE_{SM}) were discussed. The CARE_{SM} Program was constructed to help ensure that when Plan B® was OTC for one age group and prescription for another that it would be provided responsibly and appropriately. Duramed resubmitted their application on August 17, 2006 and included revised prescription and OTC labeling for Plan B® along with a revised CARE_{SM} Program. Dr. Andrew von Eschenbach wrote, in a memorandum dated August 23, 2006, that the scientific data supported an OTC indication for women aged 17 years and older. However, he stated:

“In considering the difficulty of enforcing an age-based restriction on the availability of this oral hormonal contraceptive, I have concluded that 18 (rather than 17) is the more appropriate cutoff point to best promote and protect the public health. The state-regulated pharmacies that will be dispensing Plan B® under Barr’s voluntary CARE_{SM} program (as well as society as a whole) are more familiar with 18 as a cutoff age. I understand that in all 50 states, 18 is the age of majority (i.e., the legal delineation between minor and adult), and retail outlets, including pharmacies, are familiar with using 18 as the age restriction for the sale of certain products..... This approach builds on well-established state and private-sector infrastructures to restrict certain products to consumers 18 and older..... Here, Barr’s

CARESM program specifically utilizes state-licensed pharmacies to implement its restricted distribution plan. Given this fact, and the existing experience pharmacies have enforcing the age-based restriction of 18, I have determined that to best protect and promote the public health nonprescription Plan B[®] should be available for ages 18 and above.”

Plan B[®] was approved OTC for women ages 18 years and older on August 24, 2006. It remained available by prescription for those less than 18 years of age. As Dr. Furlong points out in her review, Plan B[®] thus became the only FDA-approved contraceptive product with OTC labeling for a subset of women for reproductive age. In contrast, condoms and spermicides have a long history of OTC availability without regard to age.

Between 2007 and 2010, FDA had a variety of meetings (internal and with the sponsor) and other communications with Duramed regarding the data needed to support the unrestricted OTC availability of Plan B[®] and Plan B[®] One-Step. Dr. Galson, Dr. Jenkins, others from management and representatives from the Pediatric and Maternal Health Staff participated in some of those discussions and provided input into the trial design requirements for label comprehension and actual use studies to be conducted in adolescents. Thus, when I signed letters advising the sponsor as to study parameters such as how many young people of each age to enroll in the trials, much of this advice had been vetted by others higher in the Agency than I and by our pediatric consultants so we were sure the advice addressed Dr. Galson’s concerns.

On January 12, 2009, Duramed submitted NDA 21-998 to support the nonprescription approval of Plan B[®] One-Step for women at least 18 years of age and the prescription approval for women less than 18 years old. (This was the second round of FDA review for this application.) During the course of the review, on March 23, 2009, the U.S. Federal District Court Judge Edward Korman (in the case of *Tummino v. von Eschenbach et al*) issued an order directing the FDA to permit Duramed to make Plan B[®] available to women ages 17 years and older without a prescription within 30 days. In addition, he ordered FDA to reconsider its decisions regarding the Plan B switch to OTC use.

On April 21, 2009, I signed a letter to Duramed on behalf of FDA and in alignment with the court order which said,

“As you were advised in a letter dated August 26, 2005, the Center for Drug Evaluation and Research concluded that the available scientific data were sufficient to support the safe use of Plan B[®] as a nonprescription product for women who are 17 years or older. When FDA made the determination in 2006 to approve nonprescription availability for women 18 years or older, the reason provided for not approving nonprescription access for 17-year-old women was a concern expressed by the Commissioner about the ability of pharmacies (and thus their professional staffs) to enforce the age restriction with respect to purchases by women under age 17 without a prescription.

The Center has been authorized to handle this application using the same procedures as for other drugs, as described in the current delegation procedures. Therefore, as the Division Director, I have now considered whether the enforceability concerns expressed by the

Commissioner necessitate an age restriction to women 18 years of age and older for nonprescription use as opposed to a restriction to women 17 years of age and older. I am unaware of data that support a distinction between ages 17 and 18 in terms of enforceability of an age restriction. Data recently submitted by you regarding your Convenient Access, Responsible Education (CARE) program, under which you have monitored compliance with the current prescription age requirement, support the fact that pharmacists do check identification for the age restriction as it exists today. I have no reason to doubt that pharmacists are capable of accurately determining the age of women seeking to purchase Plan B® without a prescription by reviewing identification and providing Plan B® according to the conditions of approval as related to age. I therefore conclude that Plan B® may be made available to women 17 years and older without a prescription.”

The letter also said that if Duramed wanted to pursue marketing of Plan B® for women 17 years of age and older without a prescription but prescription only for women 16 years and younger, they would need to submit revised draft labeling as a prior approval efficacy supplement to NDA 21-045 that would allow for this change in population. Additionally, in the letter, FDA told Duramed that if they wanted to pursue the marketing of Plan B® for women 17 years of age and older without a prescription, or other options for marketing Plan B®, that FDA encouraged a meeting to discuss necessary labeling revisions and the content of any submission(s).

On June 1, 2009, Duramed met with FDA to discuss the pathway to a full OTC switch for both the Plan B® and Plan B® One-Step products. At that meeting, Duramed explained that any future drug development plans would be dependent upon the decisions of Teva management. Duramed stated that any decision regarding changes to the labeled population, beyond an OTC switch for women 17 years of age, would occur after the July 12, 2009 PDUFA goal date for NDA 21-998. FDA and Duramed agreed that, for NDA 21-045, the sponsor would provide an efficacy supplement with revised labeling and a safety update to support OTC access down to 17 years of age. Similarly, the sponsor would amend NDA 21-998 for Plan B® One-Step by providing revised labeling for OTC access to 17 years of age and also the requisite safety update. Within two weeks, Duramed submitted all of this material and on July 10, 2009 both products were approved OTC for women down to age 17.

Now, with this new efficacy supplement, Teva seeks OTC availability of Plan B® One-Step for all women of reproductive age. Teva is not currently marketing Plan B® in the United States, so the company is not seeking the same marketing status for that product. There are two companies (Watson and Perrigo) that currently market generic versions of Plan B® in the U.S.

3. CMC/Device

There were no new chemistry data required for this efficacy supplement. The drug product and the packaging are identical to the approved product.

4. Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology issues were raised in this efficacy supplement and thus no new pharmacology/toxicology studies were required or submitted.

5. Clinical Pharmacology/Biopharmaceutics

There are no new clinical pharmacology/biopharmaceutics issues raised by this efficacy supplement and thus no new data were required or submitted.

6. Clinical Microbiology

There were no clinical microbiology data required and none were submitted for this efficacy supplement.

7. Clinical/Statistical-Efficacy

The efficacy of Plan B® One-Step was established for all females of reproductive age for the original NDA approval. The product is approved both as an OTC and as a prescription drug based upon these efficacy data that demonstrated the prevention of an acceptable fraction of pregnancies (83.95%) when the product is used within 72 hours of unprotected coitus. Therefore, no new clinical efficacy data were needed to support the approval of this efficacy supplement to switch the product from prescription to OTC for young women < 17 years of age.

8. Safety

Study DR-LEV-301: Label Comprehension Study (LCS)

For the detailed analysis of the Label Comprehension Study the reader is referred to the Social Scientist review by Oluwamurewa Oguntimein and the statistical review by Dr. Rima Izem. Dr. Izem stated that she “reproduced the applicant’s findings from the provided dataset.” Thus, the reported analyses of the data were accurate according to the protocol and the statistical analysis plan.

This was an open-label, non-comparative multi-center study designed to estimate the proportion of young women aged 12-17 years who understood each of the following key elements of the Plan B® One-Step labeling:

1. Plan B® One-Step is indicated for prevention of pregnancy after unprotected sex
2. Plan B® One-Step should be taken as soon as possible after sex
3. Plan B® One-Step does not prevent sexually transmitted diseases or HIV/AIDS
4. Plan B® One-Step should not be used in place of regular contraception

5. Plan B® One-Step should be taken within 72 hours after sex
6. Plan B® One-Step should not be used by women who are already pregnant

Two to four questions were posed to test each element. Three hundred seventy-seven subjects were recruited of whom 335 met all inclusion criteria and comprised the primary analysis population. They were recruited at eight shopping malls (n = 290) and family planning clinics sites (n = 45) spread across the United States. Minimum quotas were pre-specified to ensure diversity by age, race, literacy, and prior EC use. The quotas for race and ethnicity were based on U. S. census data from the year 2000; the quota for literacy was based on the 2002 National Assessment of Adult Literacy.

The planned analysis was the proportion of subjects who understood each key concept for the overall population and for a variety of predefined subgroups. The sample size for each age range, other subgroup quotas, and the elements of labeling to test were negotiated with the FDA before the study started.

The pre-specified demographic quotas were met and exceeded. The eligible population included between 54 and 59 subjects of each age between 12 and 17 years of age (see Table 1). The FDA had requested that the sponsor enroll at least 50 of each age. Among the eligible population, 21% were Hispanic, 26% were African Americans, and 42% were low literate defined as reading at a 7th grade level or less (as assessed with a score of 58 or below on the Rapid Estimate of Adult Literacy in Medicine – Teen instrument). Seven percent reported previous use of emergency contraceptive pills, although the protocol allowed for up to 25%.

Table 1. Eligible Population by Age Group

Age	N
12	54
13	56
14	54
15	59
16	57
17	55
Total	335

Source: Dr. Furlong’s review

Table 2 demonstrates that the least well understood concept was that Plan B® One-Step should be taken as soon as possible after sex (82.7%). (While recognizing differences in methodology and the hazards of cross-study comparisons, in the label comprehension study for Plan B® which supported the OTC switch for women at least 18 years of age, the comprehension rate for this communication objective was also 82%.) The other concepts were understood by ≥ 89.6%. These are quite good comprehension rates for a label comprehension study. They compare favorably to LCS results that have supported the approval of other OTC products, among these Plan B® for adults. (Refer to Table 1 on page 9 of Dr. Karen Lechter’s review of the LCS for Plan B®.)

Table 2. Study Subjects Understanding of Key Concepts

Key Concepts	Subjects who understand n (%) N=335	95% CI
1. 1. Plan B® One-Step is indicated for prevention of pregnancy after unprotected sex	300 (89.6%)	(86%, 93%)
2. Plan B® One-Step should be taken as soon as possible after sex	277 (82.7%)	(78%, 87%)
3. Plan B® One-Step does not prevent sexually transmitted diseases or HIV/AIDS	310 (92.5%)	(89%, 95%)
4. Plan B® One-Step should not be used in place of regular contraception	309 (92.2%)	(89%, 95%)
5. Plan B® One-Step should be taken within 72 hours after sex	319 (95.2%)	(92%, 97%)
6. Plan B® One-Step should not be used by women who are already pregnant	320 (95.5%)	(93%, 97%)

Source: Adapted from Dr. Izem’s review

Table 3 shows that the understanding of key concepts was similar regardless of the age of the adolescent. Key concept #2, related to timing of pill ingestion, trends to being less well understood by 12- and 13-year-olds. In retrospect, the scenario question testing this key concept was probably confusing to the study participants. The scenario-based question was,

(b) (4)

The social scientist review provides the following analysis of this question and the responses to it.

“Per protocol, the correct answer was “Thursday night”; however, the question is ambiguous. A better question would have been “when was the best time to buy it and take it.” The data show that some subjects chose “Saturday” or “it doesn’t matter” because Saturday was as soon as Ellie could have taken the product given the time of purchase. These subjects explained their choice with “It works best if used ASAP,” “the sooner the better,” “because she should have bought it before,” and “because that’s when she bought it.” Although these subjects chose a response that was incorrect per protocol, they appear to have understood the concept. Among those subjects who answered “Saturday” as the best time to take the product, 81% (43/53) indicated that the reason they chose that day was because it was within the 72 hours (three days) limit that was written on the box. In addition, 10 out of the 19 subjects who answered “Doesn’t matter” also indicated that the reason they chose “Doesn’t matter” was because the two options “Thursday” and “Saturday” are both within the 72 hours (three days) limit that was written on the box.”

The social scientist notes that subjects performed better on a clearer, more direct question testing Key Concept #2:

(b) (4)

The correct answer “Right away” was chosen by 87.2% of subjects. Arguably, the scenario-based question likely resulted in an underestimation of the understanding of this key concept, and the responses to direct questioning (87.2%) more realistically reflect the understanding of Key Concept #2.

Furthermore, the subjects appeared to understand key concept #5, also related to timing of pill ingestion, as well as the older teenagers did. I agree with the review team that the importance of the “abstract” Key Concept #2 is diminished by the excellent comprehension of Key Concept #5. It is important to note that in the Actual Use Study (see Table 8 below), no participants less than age 13 (and only three aged 13) presented to clinic study sites seeking EC. It is highly likely that these young adolescents will be a very small minority of users if the product is available to them OTC. In response to the LCS results, with this efficacy supplement the sponsor has added prominent text to the proposed label to emphasize the importance of taking Plan B® One-Step as soon as possible.

Table 3. Understanding of Key Concepts by Age

	Age					
	12 N= 54 %	13 N= 56 %	14 N= 54 %	15 N= 59 %	16 N=57 %	17 N=55 %
1. Plan B® One-Step is indicated for prevention of pregnancy after unprotected sex	87	82	85	95	91	96
2. Plan B® One-Step should be taken as soon as possible after sex.	78	77	83	88	83	87
3. Plan B® One-Step does not prevent STDs or HIV/AIDS	91	88	87	98	95	96
4. Plan B® One-Step should not be used in place of regular contraception	93	88	91	93	93	96
5. Plan B® One-Step should be taken within 72 hours after sex.	98	89	89	98	98	98
6. Plan B® One-Step should not be used by women who are already pregnant	94	95	91	98	97	98

Source: Dr. Furlong’s review

White participants trended toward understanding the key concepts somewhat better than African Americans and others but the success rates across all groups were quite good. (See Table 4.) Hispanic ethnicity did not seem to impact label comprehension, except possibly for a trend toward greater understanding of key concept #2 among Hispanics. (See Table 5.) Lower literate subjects trended toward less understanding of all six key concepts (See Table 6.) Subjects who had prior experience with emergency contraceptives tended to have somewhat better comprehension of key concepts than subjects who had never used ECs. (See Table 7.)

Table 4. Understanding of Key Concepts by Race

	White only	Race African American	Other
	N= 163	N= 88	N=74
	%	%	%
1. Plan B® One-Step is indicated for prevention of pregnancy after unprotected sex	95	88	89
2. Plan B® One-Step should be taken as soon as possible after sex.	90	73	87
3. Plan B® One-Step does not prevent sexually transmitted diseases or HIV/AIDS.	97	91	92
4. Plan B® One-Step should not be used in place of regular contraception	97	90	92
5. Plan B® One-Step should be taken within 72 hours after sex.	98	94	100
6. Plan B® One-Step should not be used by women who are already pregnant	98	98	96

Source: Dr. Furlong’s review

Table 5. Understanding of Key Concepts by Ethnicity

	Hispanic	Non-Hispanic
	N= 70	N= 254
	%	%
1. Plan B® One-Step is indicated for prevention of pregnancy after unprotected sex	93	92
2. Plan B® One-Step should be taken as soon as possible after sex.	93	83
3. Plan B® One-Step does not prevent STDs or HIV/AIDS	94	95
4. Plan B® One-Step should not be used in place of regular contraception	93	94
5. Plan B® One-Step should be taken within 72 hours after sex.	100	97
6. Plan B® One-Step should not be used by women who are already pregnant	97	98

Source: Dr. Furlong’s review

Table 6. Understanding of Key Concepts by Literacy Level

	Literacy Level	
	7th grade or lower N= 140 %	8 th grade or higher N= 195 %
1. Plan B® One-Step is indicated for prevention of pregnancy after unprotected sex	82	95
2. Plan B® One-Step should be taken as soon as possible after sex.	74	89
3. Plan B® One-Step does not prevent STDs or HIV/AIDS	84	99
4. Plan B® One-Step should not be used in place of regular contraception	87	96
5. Plan B® One-Step should be taken within 72 hours after sex.	92	97
6. Plan B® One-Step should not be used by women who are already pregnant	92	98

Source: Dr. Furlong’s review

Table 7. Understanding of Key Concepts by Ever Use of Emergency Contraceptive Pills,

	Prior use	Never used
	N= 24 %	N= 311 %
1. Plan B® One-Step is indicated for prevention of pregnancy after unprotected sex	100	89
2. Plan B® One-Step should be taken as soon as possible after sex.	83	83
3. Plan B® One-Step does not prevent sexually transmitted diseases or HIV/AIDS	100	92
4. Plan B® One-Step should not be used in place of regular contraception	96	92
5. Plan B® One-Step should be taken within 72 hours after sex.	100	95
6. Plan B® One-Step should not be used by women who are already pregnant	100	95

Source: Dr. Furlong’s review

Teva also provided a comparison between Study DR-LEV-301 and the LCS done in 2001 for the Plan B® application. The 2001 study included 656 subjects from 12 to 50 years old, of whom 580 were 17 years and older. The 2001 study was of similar design and 13 questions in both studies overlapped. The proportions of subjects who answered correctly were similar for 11 of 13 questions. In the two questions with the greatest difference between groups, the older subjects had a greater percentage of incorrect responses. Both of these questions were related to the instruction to take the tablets as soon as possible after sex.

My assessment of the label comprehension study results is in agreement with those of Ms. Oguntimein, Dr. Chang, and Dr. Furlong. The study was well-designed with an adequate sample size and demonstrated that adolescents had an acceptable understanding of the key

labeling elements. The study was designed and conducted in keeping with the advice the sponsor received from the FDA and accounted for Dr. Galson's concerns. Likewise, Dr. Lisa Mathis, Associate Director of the Pediatric and Maternal Health Staff in the Office of New Drugs, did not express concerns with the study or the results.

I agree with Drs. Chang and Furlong, both of whom are obstetricians/gynecologists with many years of clinical practice experience, that from the clinical perspective, the importance of the lower understanding of Key Concept #2 in the youngest teens is diminished by their solid comprehension of the message to take the medicine within 72 hours after sex. As long as element #5 is understood, efficacy should not be unacceptably compromised. I agree with the reviewers that with OTC access, the time between a contraceptive failure and obtaining EC may be shortened (compared to the time needed to obtain a prescription) and could allow for easy compliance with the 72-hour time window.

That "as soon as possible" was also less well understood by older subjects in the label comprehension study for Plan B® conducted in 2001 suggests that there is something about the lack of precision of the language that makes the message harder in general to understand. As Dr. Furlong points out, "With the caveat that cross-study comparisons have pitfalls, historical data from a similar study for Plan B® found a greater percentage of generally older subjects had a lower understanding of element 2 ("as soon as possible") than the younger subjects in the Plan B® One-Step study."

Regarding the low literate performance, as Dr. Furlong comments, "The comprehension of key elements in this LCS is akin to the numbers seen in LCS studies that have supported approval of other OTC products." In label comprehension studies we usually see low literacy numbers that are a little less robust than those of the general population. Most OTC labels are written with an attempt to target no higher than an 8th grade literacy level. The comprehension results demonstrated by subjects of low literacy in this study are in the general range for low literacy data in other label comprehension studies that have supported OTC drug approvability.

DR-LEV-302: Actual Use Study (AUS)

Label comprehension studies are conducted to achieve a well-understood product label. If people can comprehend what they read and apply the information on the label this will help them when using or considering use of the medication. However, success with a label comprehension study does not necessarily predict appropriate product use. Behavior with Plan B® One-Step was assessed with Actual Use Study DR-LEV- 302.

The actual use study is reviewed in detail in Dr. Chang's primary clinical review and was also assessed by Drs. Furlong and Mathis. Dr. Izem performed a statistical review of the AUS and stated that the statistical review "reproduced the applicant's findings for the primary endpoints" from the provided datasets. Thus, the reported analyses of the data were accurate according to the protocol and the statistical analysis plan.

The AUS was an open-label, single-arm, naturalistic study to determine the percentage of subjects who correctly self-select and use Plan B® One-Step under simulated OTC conditions. The two primary objectives of the study were:

- to determine the percentage of subjects who appropriately self-selected
- to determine the proportion of subjects who correctly used Plan B® One-Step under simulated OTC conditions

Correct self-selection was defined as wanting to use the product for its indication AND not having an allergy to levonorgestrel, a positive pregnancy test, or a known pregnancy. Correct use was defined as taking Plan B® One-Step within 72 hours following unprotected sex. The secondary objectives were to estimate the incidence of adverse events and repeat use of emergency contraception during the 8-week follow-up period.

The study sought to enroll subjects 11 to 17 years old who were seeking emergency contraception (EC). The setting mimicked the OTC environment in that subjects who had self-diagnosed the need for EC presented to the clinic study sites spontaneously requesting EC and obtained Plan B® One-Step without the intervention of a healthcare provider. Each subject who met the inclusion criteria (age, need of EC for herself, ability to read English, and willingness to participate in the study) read the product label without assistance. A pre-approved script controlled the information that study staff could provide. Only those subjects who appropriately self-selected (as assessed via a self-administered Participation Questionnaire following the self-selection decision) received study medication. Subjects who inappropriately self-selected were referred to clinic staff for further assessment and treatment.

Follow-up occurred at one, four, and eight weeks, and weekly thereafter if needed for adverse events or pregnancies. Subjects were asked about product use, health problems since last contact, and pregnancy status. Subjects were also asked about repeated use of EC since enrollment, and charts were evaluated for repeat use as well.

The sample size (which had been negotiated with FDA) was to include a minimum of 25 females of each age, 14 through 17 years, and any subjects from 11 to 13 years who were eligible to participate. The originally agreed-upon number of subjects in the 11- to 13-year age range was 25, but, after two years of study experience, enrollment in that age range was minimal (only three subjects aged 13 and none younger than 13). FDA agreed to a protocol amendment to continue to enroll 11- to 13-year olds without a minimum number of enrollees after the applicant presented their interim enrollment data and provided literature showing that difficulty enrolling younger subjects was to be expected. Refer pages 49-50 of Dr. Chang's review for the details. When Plan B® One-Step was approved in July 2009 as an OTC product for women 17 years of age and older, the AUS protocol was amended to no longer recruit 17-year-olds.

Results:

Enrollment was slow because the Actual Use Study was initiated prior to the approval of Plan B® One-Step, while the drug was still an investigational product. However, the University of California, San Francisco site was able to enroll study participants during that period. After the drug was approved, Teva increased the number of participating sites and ultimately, there were five geographically dispersed clinical investigation sites; however, the one at the University of California still enrolled the vast majority of the study participants (316 of 343 total subjects). The fact that the University of California site enrolled a diverse, representative population

makes the study population enrolled in this trial acceptable. The FDA Office of Scientific Investigation inspected this site and found that “the efficacy and safety data for this Actual Use Study are considered reliable.” (Refer to Section 10 below.)

Table 8 depicts the age range of enrolled subjects. It is important to point out that clinics were unable to enroll any subjects younger than 13 years of age because none presented for emergency contraception. As Dr. Mathis comments in her review, the low number of adolescents from ages 11 – 13 years old is consistent with the known use of these products in this age group. She states, “The condition and the response to therapy in patients in this age group is expected to be sufficiently similar to patients in the 14-year-old age group and thus data from that age group can be used to support the ability of younger patients to use the medication appropriately.” While there were few enrollees less than 14 years old, the LCS enrolled 50 subjects aged 12 and 50 aged 13 and their comprehension of the label was good. (Refer back to Table 3.) The race distribution was 42.9% Latina, 19.8% Asian/Pacific Islanders, 14.0% African-American, and 11.4% White.

Approximately 40% of subjects had used EC previously, with the percentage increasing with age (ranging from 0% of 13-year-olds, to 66.2% of 17-year-olds). As shown in Table 8, approximately 29.4% of subjects reported no previous use of contraception with the percentage decreasing with increasing age (66.7% of 13-year-olds to 15.4% of 17-year-olds). Approximately 88.3% had never been pregnant, with the percentage decreasing with increasing age (100% of 13-year-olds to 81.5% of 17-year-olds).

Table 8. Number of Subjects and Prior Use of Contraception by Age in AUS

Age of Subjects	13 years old	14 years old	15 years old	16 years old	17 years old
N	3	35	100	140	65
No previous use of contraception	66.7%	51.4%	31%	28.6%	15.4%

Source: Applicant’s Submission, Clinical Study Report, Table 8

By the applicant’s analysis, results of the primary objectives for the enrolled population were:

- 90.1% appropriately self-selected
- 88.6% of those who appropriately self-selected correctly used the product within 72 hours of intercourse

Dr. Chang’s performed a detailed analysis of reasons for inappropriate self-selection, and the expected consequences. She found that Teva’s definitions of inappropriate self-selection and use were conservative, particularly when the clinical consequences are considered and I agree with her. For example, the most common reason that resulted in Teva coding adolescents as inappropriate self-selectors (25 of 34 subjects) was “might be pregnant.” Upon a closer look though, subsequent verbatim responses suggested that many of these adolescents thought they “might be pregnant” from the index episode of unprotected sex; therefore, these adolescents, if they chose to use the product, would actually be correct in doing so. For example, one 14-year-old said, “Just in case I was pregnant because when I was having intercourse the condom ripped.” It is noteworthy that these subjects that Teva coded as inappropriate self-selectors had

not taken a pregnancy test. Also, these adolescents stated later in the questionnaire that they were not pregnant.

In Dr. Chang’s review, she considered only two subjects of the 343 to be inappropriate self-selectors because they had positive pregnancy tests at the time of self-selection. This means that there was a > 99% correct self-selection rate, which I think is excellent. As Drs. Chang and Furlong point out, although these two subjects would derive no benefit from the use of Plan B® One-Step, the risks of doing so are minor particularly since product use would not impact the course of an established pregnancy.

Similarly, Dr. Chang’s analysis of the reasons Teva coded users as incorrect showed that the applicant’s definition of incorrect use was conservative. I agree with this, as well. Dr. Chang found that the applicant coded eleven subjects as incorrect users because the subjects did not follow-up within 10 days of the clinic visit; however, these eleven subjects used Plan B® One-Step correctly (that is, within 72 hours of the index episode of unprotected sex). Excluding these subjects from the “incorrect user” population gives a correct use percentage of 92.3%. (Refer to page 43 of Dr. Chang’s review.) This is very close to the findings of the AUS study conducted to support the OTC switch of Plan B®, where 92.4% of subjects in this mostly adult population took the first of the two doses of Plan B® within 72 hours of unprotected intercourse. Dr. Chang points out that, concerns regarding cross-study comparisons notwithstanding, adult and adolescent subjects appear to have used EC comparably well in these two studies, and this argues compellingly for removing age restriction at the point of purchase.

Table 9 and Table 10 show exploratory analyses of the primary endpoint by age. Overall, there are no clear trends by age.

Table 9. Proportion of Enrolled Population that Appropriately Self-Selected by Age (Years)

	13	14	15	16	17
Number of Subjects	3	35	100	140	65
Appropriate Self-Selection	2 (66.7%)	30 (85.7%)	91 (91.0%)	128 (91.4%)	58 (89.2%)

Source: Applicant’s Submission, Clinical Study Report, Table 18

Table 10. Proportion of Treated Population Demonstrating Correct Product Use Within 72 Hours after Intercourse by Age (Years)

	13	14	15	16	17
Number of Subjects	1	30	87	123	56
Product Use within 72 Hours	1(100%)	24 (80.0%)	78 (89.7%)	107 (87.0%)	53 (94.6%)

Source: Applicant’s Submission, Clinical Study Report, Table 19

Refer to page 41, Table 21 of Dr. Chang’s review. She notes that naive and experienced EC users did as well using the product correctly. Potential users, whether naive or experienced, can successfully follow the directions for use on the product box.

I agree with the clinical review team that results support that the large majority of teens can use OTC labeling to appropriately self-select and use Plan B® One-Step. There was no clear

trend in proportion of correct self-selection or correct use by age, although a larger number of older teens than younger teens sought to use Plan B® One-Step. (As indicated above, the lower number of 17-year-old enrollees was the result of a protocol amendment that stopped recruitment of 17-year-olds after Plan B® One-Step was approved as an OTC product for women 17 years of age and older.)

A secondary objective was measuring the repeat use of emergency contraception during the 8-week follow-up period. Most subjects reported a single use of Plan B® One-Step during the study. Table 11 summarizes a subgroup analysis by age. There was no discernable trend for repeat use by age. Repeat use included one additional time (13.7%), two additional times (5.7%), or three additional times (0.7%).

Table 11. Repeat Product Use in the Completed Follow-Up Population (N=277) by Age (Years) at Screening

Number of repeat uses	13	14	15	16	17
None	1 (100%)	22 (84.6%)	64 (78.1%)	92 (81.4%)	45 (81.8%)
1	0	1	12	19	6
2	0	3	6	3	4
3	0	0	1	1	0

Source: Applicant’s Submission, Clinical Study Report, Table 28

I agree with Dr. Furlong that this analysis of repeat use adequately addressed Dr. Galson’s concern that teens might substitute the product for routine and more effective contraception. The repetitive EC uses were few for all age groups studied over the 8-weeks. Dr. Chang writes, “...considering the likely consequence of irregular bleeding associated with repetitive, intermittent progestin use and the prohibitive cost of EC (more than a monthly package of generic oral contraceptives),” that she would not expect to see long-term substitution of EC for routine oral contraception. I would comment that FDA does not consider cost as a factor in the decision making process for drug approval, but I agree that irregular bleeding would probably be a deterrent to frequent use of EC.

However, Dr. Furlong goes farther in stating that she thinks Dr. Galson’s concern was misplaced and I agree with her. Dr. Furlong correctly makes the point that “it is not within FDA’s purview to require that a person use the most effective birth control method available (or, for that matter, the most effective antihypertensive or heartburn drug available). Condoms are not the most effective contraceptives, but FDA does not restrict access to condoms because condoms may be substituted for more effective methods. It is also not within the FDA’s purview to require that routine contraception be used by sexually active people. The decision to use birth control and the choice of birth control method depend on many factors (sexual frequency, level of concern about pregnancy, price, access, concern about sexually-transmissible infection, contraindication to a particular method, to name just a few.) For the youngest teens in the study, most had used no contraception in the past. Use of Plan B® One-Step once or intermittently can be a reasonable choice.”

Adverse Events (AEs): Of the 297 subjects who took study drug, 43 reported a total of 70 AEs. There were no deaths and one serious adverse event was reported (a miscarriage). As Dr. Furlong notes, miscarriage is a common outcome of pregnancy and the relationship of this event to Plan B® One-Step could not be definitely established. Other adverse events were reported infrequently and there were no unexpected or worrisome findings. Because of the single arm nature of the actual use study, the contribution of drug to the adverse events reported is unclear. The most frequently reported adverse events were nausea, headache, and menstrual irregularity. (Refer to Table 12.)

Table 12. Frequency of Reported Adverse Events in $\geq 1\%$ of the Safety Population: Subjects Who Reported Any Use of Plan B® One-Step

Adverse Event (MedDRA Preferred Term)	Total Number of Subjects = 299 N (%)
Nausea	8 (2.7%)
Headache	8 (2.7%)
Menstruation Irregular	6 (2.0%)
Vaginal Bleeding*	4 (1.3%)
Pelvic Pain	4 (1.3%)
Influenza	3 (1.0%)
Vulvovaginal Mycotic Infection	3 (1.0%)
Vaginal Spotting*	3 (1.0%)
Dizziness	3 (1.0%)
Abdominal Pain Upper	3 (1.0%)
Fatigue	3 (1.0%)
Vomiting	3 (1.0%)

*Vaginal Bleeding, regardless of severity, codes in MedDRA to a Preferred Term of “Vaginal Haemorrhage.” Therefore, for clarity, the applicant used the MedDRA Lower Level Term rather than the Preferred Term
Source: Applicant’s Submission, Clinical Study Report, Table 29

Subjects reported seven pregnancies, one of which was reported by investigators as a serious adverse event (the miscarriage). The pregnancy data are summarized in Table 13.

Table 13. Summary of Pregnancies Among the 297 Subjects Who Took Plan B® One-Step

Site/Subject	Age (Years)	Used Plan B® within 72 hours of unprotected intercourse	Comments	Outcome
1/0107	16	Yes (one day after unprotected sex)	By 8-week ultrasound, conceived on or shortly after the index episode of unprotected sex	Surgical termination
1/0131	14	Yes (one day after episode of unprotected sex for which she presented to the clinic)	By 13-week ultrasound, was about 1 week pregnant when she took Plan B® One-Step (too early for self-diagnosis or positive pregnancy test). Information was not provided to clarify if she had another episode of unprotected sex prior to the one that triggered her visit to the clinic.	Surgical termination
1/0302	17	Yes (two days after unprotected sex)	By 7-week ultrasound, conceived shortly after the index episode of unprotected sex.	Surgical termination
1/0362	16	Yes (two days after unprotected sex)	By 7-week ultrasound, conceived on or shortly after the index episode of unprotected sex.	Surgical termination
1/0384	16	Yes (one day after unprotected sex)	By 26-week ultrasound, conceived after the index episode of unprotected sex	Delivered healthy infant at 36.5 weeks gestation
1/0405	16	Yes (one day after unprotected sex)	By 7-week ultrasound, conceived on or shortly after the index episode of unprotected sex	Ongoing pregnancy
1/0502	16	Yes (one day after unprotected sex)	Negative pregnancy test two weeks after taking Plan B® One-Step; positive 3 weeks after taking Plan B® One-Step; therefore, likely conceived after the index episode of unprotected sex.	Miscarriage

Source: Dr. Furlong’s review

Dr. Furlong concludes that the pregnancy data do not support a relationship of age to lack of efficacy or a lack of efficacy related to inappropriate use. Dr. Chang notes that “given the range of possible conception dates derived from ultrasound findings, it is quite likely that four of the pregnancies were conceived after the index episodes of unprotected sex.” By ultrasound dating, subject 10131 may have been pregnant when she took Plan B® One-Step, but she was too early in gestation (1 week post conception) to have missed a period and suspected pregnancy. Drs. Chang and Furlong conclude that her use of Plan B® One-Step was, therefore, appropriate and I agree. All women who became pregnant used Plan B® One-Step as directed on the OTC labeling. It is important to remember that some pregnancies are expected to occur despite correct use: Plan B® One-Step reduces, but does not eliminate, the

chance of pregnancy after unprotected sex. In clinical trials, approximately 84% of expected pregnancies were prevented.

Assessment:

It is clear from the AUS that the vast majority of teens were able to correctly self-select and use Plan B® One-Step. The safety profile was consistent with what we know about this product and without unexpected signals of concern. Therefore, adolescents should be expected to have a favorable risk/benefit profile if the product is available OTC. I agree with Drs. Chang, Furlong, and Mathis that that the Actual Use Study results support OTC availability for adolescents.

Postmarketing Spontaneous Reports

Refer to Dr. Christina Chang’s review for a comprehensive look at the postmarketing safety databases. Of 69 countries in which levonorgestrel 1.5 mg is legally marketed, 32 market the product as a nonprescription drug. There have been no regulatory or marketing authorization actions taken for safety reasons, and the product has not been withdrawn from or restricted in any market for safety reasons. Between Jul-09 and Jan-11, approximately 3.5 million tablets of Plan B® One-Step were distributed in the United States.

The applicant provided summaries of postmarketing reports from these databases:

- Teva’s Internal Database (10-Jul-2009 through 30-Nov-2010)
- The World Health Organization (WHO) database (10-Jul-2009 through 15-Feb-2011)
- The FDA’s AERS database (10-Jul-2009 through 30-Sep-2010)
- 120-day safety update
- DAWN
- AAPCC

An analysis of the postmarketing databases did not detect any new or unexpected safety signals in women of any age and no evidence of unique safety issues were found in adolescents. A brief summary of the postmarketing data by database follows.

Teva’s Internal Database

The applicant reviewed the internal postmarketing safety database for Plan B® One-Step from the time of approval on July 10, 2009 through Nov 30, 2010. The search included the age range of 9 to 16 years. The youngest reporter was 13 years old. There were 332 events reported by 186 users, representing 2.4% of all events reported for the time period. The pattern of events did not show any additional risk in the younger population. One subject reported a serious, unlabelled event: vomiting blood (hematemesis). Reports of hematemesis are discussed in more detail later in my review. Table 14 shows that adverse event profiles were similar for adolescents compared with all women.

Table 14. Comparison of the Most Frequent AEs in Adolescents with All AEs Regardless of Age

Adverse Event	Most Frequent Adverse Events in Adolescents 13 – 16 years	All Adverse Events Regardless of Age
Menstruation Irregular	106	4959
Pelvic Pain	25	955
Vomiting	24	628
Nausea	22	940
Menstruation Delayed	19	546
Abdominal Pain	18	513
Headache	18	440

Source: Composite of information from Dr. Furlong's review.

WHO Database

The applicant requested a search of the WHO VigiBase for reports for levonorgestrel 1.5. mg from 10-Jul-2009 through 15-Feb-2011. A total of 369 cases reporting 969 events were obtained. Among these 369 cases, 5 were in adolescents aged 16 and under. No age specific adverse events were noted. Two of these cases overlapped with the AERS database. The remaining three reports were of breast disorder, ectopic pregnancy, and fetal abnormality (not otherwise specified).

AERS Database

The applicant conducted a search of the AERS database from July 10, 2009 to 30-Sep-2010 for Plan B®, Plan B® One-Step, and other levonorgestrel-containing emergency contraceptive products (ECs). For all women, there were 71 cases reporting 303 adverse events for Plan B® and Plan B® One-Step, and an additional 28 cases reporting 66 adverse events for other levonorgestrel ECs. A total of four cases were identified in young women aged 16 and under; all reporters were 15 or 16 years of age. The four cases reported hypersensitivity-type reaction, menstrual changes, emotional distress, lack of efficacy, nausea, vomiting, and hematemesis. There were no age specific adverse events.

120-Day Safety Update

No signals were detected suggesting a change in the safety profile of Plan B® One-Step or any age-specific safety issues.

DAWN and AAPCC

There is no historical evidence to suggest that levonorgestrel is a drug with abuse or even overuse potential. The DAWN database for 2004 – 2009 and the AAPCC database for 2008 and 2009 do not raise any new concerns.

Additional FDA Analyses of Postmarketing Data

During the Plan B® One-Step NDA supplement review, FDA performed a 915 review of Plan B® One-Step (Rubio). A 915 review occurs routinely 18 months after drug approval and exposure of at least 10,000 patients, whichever is later. This review for Plan B® One Step was a detailed look at postmarketing data by FDA's Office of Surveillance and Epidemiology and the Office of New Drugs, Division of Reproductive and Urologic Products (DRUP). The 915

review evaluated reports received for Plan B® One-Step from the time of approval in July, 2009 through January 2011. During the review it was found there were eighteen reports of hematemesis with both Plan B and Plan B One-Step and they were evaluated by Dr. Daniel Davis, a medical officer in the DRUP. Of these, five cases were in adolescents ages 15 – 17. These five cases are assessed in detail below. All of the eighteen cases were reported by consumers and none were confirmed by a healthcare professional. The 915 reviewers concluded that “No potential safety issues were identified in this review that would warrant any labeling changes or changes in the product’s safety profile.”

Also, during the Plan B® One-Step NDA supplement review, the Office of Surveillance and Epidemiology (OSE) Division of Pharmacovigilance II was asked by Dr. M. Diane Murphy (Director, Office of Pediatric Therapeutics in the Office of the Commissioner) and Dr. Lisa Mathis to summarize postmarketing reports of adverse events associated with the use of Plan B® and Plan B® One-Step in patients ≤ 17 years of age. They requested this review in preparation for a routine, forthcoming meeting of the Pediatric Advisory Committee (PAC). The charge of the PAC (under the Food and Drug Administration Amendments Act) is to review safety data presented to them one year after a product is labeled under the Pediatric Research Equity Act and/or the Best Pharmaceuticals for Children Act, and to make recommendations on labeling based on those data. The FDA is charged with performing a review of all safety events since marketing, and providing that review to the PAC members so they can perform their function. This January 2012 meeting will address several approved products, among them Plan B® One-Step. The request for this OSE review was not triggered by any specific safety concern, but was simply triggered by the 2009 approval of Plan B® One-Step for pediatric use by prescription.

The OSE searched the AERS database for all reports of adverse events (serious and non-serious) from January 1, 2002 up to the "data lock" date of December 31, 2010. The AERS contained 252 reports for any Plan B® (levonorgestrel) formulation. Pediatric reports represented approximately 7.5% of the total (19/252). Eighteen of these were considered to be cases with a serious outcome. The November 10, 2011 OSE review (Miller, Rothstein, Scarazzini) described fatal outcomes or serious unlabeled adverse events with Plan B® (levonorgestrel, 0.75 mg) or Plan B® One-Step (levonorgestrel 1.5 mg). The OSE review was completed after Drs. Furlong and Chang completed their reviews and thus was not described by them, so I will describe it here and will shine a light on certain cases.

Premature Births and Spontaneous Abortions:

There were three reports of premature births. It is not clear that any of these women reported as having taken Plan B® were less than 18 years old. In these cases, the babies are reported as the pediatric patients, not the mothers. The long time between the taking of Plan B® by the mothers and the birth of the babies, makes it impossible to attribute causality to Plan B®. There is no other information about the mothers or maternal behavior provided in these case reports.

- One of the premature infants died when born at 5 months gestation. This was the only death reported among the 19 pediatric reports. The 31-year-old mother of this baby had taken Plan B on an unknown date in 12/2005 and the baby was born on 05/20/2006 and died three days later.

- One mother (age unknown) took one dose of Plan B® on 1/7/09 and her baby, who was born on 08/9/2009, did well.
- The third mother (age unknown) took only one dose of Plan B® on 03/08/09 (so she did not complete the dosing regimen) and she gave birth to her baby on 10/25/09. This baby also did well.

Additionally, there were two cases of spontaneous abortion, one in a 16-year-old patient 6 weeks after taking Plan B® and the other in a 17-year-old patient less than 8 weeks after taking Plan B®. Levonorgestrel EC does not prevent all pregnancies, and the known rate of spontaneous abortions is high regardless of levonorgestrel EC use (up to 31% of pregnancies).¹ I think that Dr. Soule described this issue aptly in her 07/09/09 review of Plan B® One-Step when she stated that “given the known rate of spontaneous abortions (about 25% of all conceptions) the reports of spontaneous abortion (*with levonorgestrel EC*) are not unexpected and do not constitute a safety signal for this product.” The rate of premature births is also high, approximately 11.5%² of all live births, and the same reasoning applies.

Hospitalizations:

The November 10, 2011 OSE review provided available details on three AE reports in adolescents that led to hospitalization and four cases of hematemesis, one of which resulted in a visit to the emergency room.

Here is my analysis regarding causality based upon the information received on three patients that were hospitalized:

- One 15-year-old patient took Plan B® on 09/11/07 and had a D & C-type procedure on (b) (6) for cramping and vaginal bleeding that occurred on 09/24/07. It is not possible to attribute causality in this case.
- One 17-year-old patient, who had taken Plan B® on an unspecified date in October, 2008 was admitted to the hospital on (b) (6) to treat an acetaminophen overdose. She was released the next day. It is not possible to say that this hospitalization is due to Plan B®.
- One 16-year-old experienced severe abdominal pain and vomiting in 2004 after taking her second dose of Plan B®. She was taken to the hospital where she was treated and released. This hospitalization may have been related to drug use, but the information in the report is too sparse to know for sure. Abdominal pain and vomiting are known, labeled, adverse effects of Plan B® in women of all ages.

Hematemesis Cases:

Next, I will highlight the five pediatric cases of hematemesis. (See Table 15.) (Four cases were reported in the November 10, 2011 OSE review and five were reported in the 915 review. This difference in the number of hematemesis cases derives from the fact that one case in the 915 review was reported in January 2011, after the data lock date for the OSE review.) These patients took Plan B® or Plan B® One-Step. One patient went to the emergency room (ER) but was not admitted. None of the others reported being seen at a hospital.

Table 15. Cases of Women Reporting Hematemesis

ISR Number	Age in Years	Medication Used	Other Details
6330193	16	Plan B® 08/19/09	Nausea and vomiting 08/19/10. Vomited blood on 08/21/09. Went to ER, not admitted. As of 08/24/09 vomiting continued but no more episodes of vomiting blood. There is insufficient information in the report to assess causality.
6408595	16	Plan B® One-Step 10/05/09	Vomited blood once on 10/19/09. Pregnancy test positive. Because of the timing of the vomiting and the positive pregnancy test, it is unlikely that the hematemesis was due to levonorgestrel.
5805767	15	Plan B® 06/22/08	One episode of hematemesis 06/26/08. Insufficient information in the report to assess causality.
6231375	17	Plan B® 06/06/09	One episode of vomiting which contained a small amount of blood 06/08/09. Insufficient information in the report to assess causality.
7210172 and 7231130	17	Plan B® One-Step 12/29/10	Vomited on 12/31/10, noticed a little tiny bit of blood and the event resolved the same day.

Consistent with findings of previously conducted postmarketing reviews by FDA (Rubio and Miller), it was difficult to attribute the cases of hematemesis reported to Plan B® or Plan B® One-Step based on the subjective nature of the reporting and lack of sufficient medical information in the AERS reports. (These reports were from consumers, not from physicians or other healthcare providers.) The Rubio 915 review concluded that given the small number of events occurring over a 3.5 year span with millions of women using emergency contraception, and no healthcare provider reporting this adverse event, they did not believe there is a significant signal here. The medical officer who worked on that review, Dr. Daniel Davis, assessed that no further review or special measures are needed to evaluate hematemesis associated with levonorgestrel taken for emergency contraception.

The OSE reviewers commented that hematemesis can result from a number of clinical situations including forceful or recurrent vomiting, or ulcers in the gastrointestinal tract, and there is not sufficient clinical data from the AERS reports to suggest that Plan B® is the direct cause of the hematemesis. This is certainly true. I would like to note that, as with any medication or condition that can induce vomiting, hematemesis may be a consequence of emesis.

To create perspective and context, it is important to note that nausea and vomiting occur in up to 90% of pregnancies and, in up to 20% of pregnancies, they may continue until delivery.³ A prospective study of more than 9000 pregnant women showed that nausea and vomiting were significantly more common in primigravidas. Among the other risk factors for emesis gravidarum were less education and younger age.⁴ Hyperemesis gravidarum occurs in up to 2% of pregnancies. Hematemesis is a known complication of hyperemesis and may or may not

be associated with underlying causes, such as H. Pylori infections.⁵ Considering the risk factors above, if the youthful population of females in need of EC were to become pregnant, cases of hematemesis would be expected to occur. The rarity of the reported hematemesis with levonorgestrel EC use and the fact that there were no reports of hospitalization or need for transfusion are very reassuring and favor a good risk benefit ratio for Plan B® One-Step in the adolescent population at risk for pregnancy.

Syncope and Loss of Consciousness Cases:

As in other FDA safety reviews on levonorgestrel EC, in this OSE review there were rare reports (two) of syncope and (three) of loss of consciousness. The reviewers comment that these rare signals have been noted before. In fact, reports of 7 cases of “syncope” and 6 of “loss of consciousness” were thoroughly assessed in a 04/08/08 OSE safety review conducted on NDA 21-045 Plan B® after it was available in dual marketing status for over one year. That 04/08/08 review assessed safety in women of all ages, not just in those less than 18 years of age.

The reviewers commented that “syncope is a sudden, brief loss of consciousness (LOC) with loss of postural tone followed by spontaneous revival. Syncope and near-syncope are fairly common and recur in up to one third of people and the cause is often benign. In early pregnancy, syncope is common because of hormonal changes. Other causes include neurogenic syncope caused by a trigger of reflex-mediated withdrawal of sympathetic tone and increase in vagal tone. Increased intrathoracic pressure (due to cough, straining to void or defecate, or another Valsalva maneuver) can limit venous return and increase vagal tone, resulting in decreased cardiac output and syncope. Strong emotion, pain, fear, sight of blood, or injury can produce strong vagal stimulation, causing vasovagal syncope, which is common. Orthostatic hypotension is a common benign cause of syncope. Patients with an anxiety disorder may faint because of hyperventilation. There was a suggestion of a possible temporal relationship with Plan B® administration, with several cases occurring within 2 days of the initial dose of Plan B. However, this case series derived from the AERS database was too small to make any further conclusions.”

In summary, I agree with the OSE reviewers that we need more clinical information than was provided to enable a more robust evaluation of the syncope and loss of consciousness adverse events. Abdominal pain and pelvic pain are concomitantly reported events in some of these case reports of syncope. It is possible that strong vagal stimulation due to pain was responsible for the syncope in these cases. Lower abdominal pain is a labeled adverse event for Plan B® One-Step. The syncope/loss of consciousness case reports are uninformative regarding the emotional states of the young women involved. Yet, young women frightened by the possibility of accidentally becoming pregnant and the many associated implications can be very distressed and upset. Certainly, any proper clinical evaluation of syncope must consider psychological factors.

The Office of Surveillance and Epidemiology postmarketing evaluation found no evidence of pediatric safety concerns with Plan B®/Plan B® One-Step EC. Their review did not note significant changes in the severity of adverse events that indicate a clinically significant change in the known safety profile of levonorgestrel EC. I agree with their conclusions. The safety reviews are supportive of OTC availability of Plan B® One-Step for young women.

Literature Review

The applicant reviewed the published literature for EC use and provided references. Dr. Christina Chang analyzed the references provided by Teva and performed an independent literature review of her own. For the details, the reader is referred to pages 63 – 76 of her review. As Dr. Chang points out, there is a large body of literature now available on expanded access to EC, mostly in the form of advanced provision by a healthcare provider. The studies vary in design methodology. I agree with Dr. Chang that the body of literature demonstrates that improved access leads to more frequent and sooner use of EC after unprotected sex. The data do not support that there were increased rates of sexually transmitted infections, decreased condom use, adoption of less reliable contraceptive methods, or other negative sexual and reproductive behaviors. I agree with Drs. Chang and Furlong that the review of the literature did not detect new safety issues or safety issues specific to younger women.

Dr. Chang comments that, to date, literature has not emerged to indicate that increased EC access reduced unintended pregnancy or abortion rates on a population level. She hypothesizes that one reason for this may be that the advance provision experience has been based on the two-dose levonorgestrel regimen or another regimen such as the Yuzpe regimen. The actual use study for Plan B® supported that, while the proportion of those who took the first dose within 72 hours was 92.4%, compliance with timing of the second dose dropped to 68-72%. Study DR-LEV-02 showed that adolescents used Plan B® One-Step correctly 92.3% of the time. In general, it is known that simplicity of a medication dosing regimen is helpful in assuring compliance.

Another reason offered by Dr. Chang is that many women still fail to use EC after unprotected sex has occurred, despite the availability, and the number of women reporting unprotected sex is likely to be an underestimate because of recall bias, denial, or the desire to please investigators. Well conducted clinical trials reviewed by FDA demonstrated the effectiveness of Plan B® One-Step and of Plan B® and led to the drug approval. However, medication cannot work, if it is not used.

9. Advisory Committee Meeting

On December 16, 2003, an Advisory Committee meeting was convened for NDA 21-045/S-011 to discuss the OTC switch of Plan B®. The committee voted overwhelmingly in favor of a complete OTC switch with no age restriction for Plan B®. The committee voted (27 to 1) that the Actual Use Study data could be generalized to the overall population of potential OTC users of Plan B®. They recommended that Plan B® be switched from prescription to OTC (23 to 4 with one member having left before voting) without age restriction. Since Plan B® and Plan B® One-Step are exceedingly similar drug products and no controversial data emerged from NDA 21-998 to generate the need for another advisory committee meeting, none was held. Likewise, no controversial data emerged from this efficacy supplement, so no Advisory Committee meeting was held.

10. Pediatrics

Dr. Lisa Mathis, Associate Director of the Pediatric and Maternal Health Staff in the Office of New Drugs, reviewed the data in this application at the consultative request of the Division of Nonprescription Clinical Evaluation. After completing her review, Dr. Mathis, a pediatrician, is recommending the approval of this application to expand OTC marketing to all females of child bearing potential. She comments that this product was previously determined to be safe and effective in the pediatric population as a prescription product. She comments that the new data submitted in the Label Comprehension and the Actual Use study provide the data to demonstrate that women of child bearing potential of all ages can appropriately self-diagnose and self-administer Plan B® One-Step in the OTC setting. She also states that no new safety concerns have been identified. Dr. Mathis states that the safety and efficacy of OTC Plan B® One-Step in the adolescent population is supported by the totality of data submitted to support the application.

Consistent with the Pediatric Review Committee recommendations from April 9, 2009, a partial waiver to study premenarcheal girls was previously granted to this sponsor because they are not at risk of becoming pregnant and the use of Plan B® One-Step would not be indicated.

11. Other Relevant Regulatory Issues

There are no unresolved relevant regulatory issues.

Office of Scientific Investigation (OSI) Audit

The Office of Scientific Investigation conducted an inspection of the Actual Use Study (DR-LEV-302) site at the New Generation Health Center in San Francisco, CA 94110. This site enrolled 316 subjects, far more than any other site in the study.

Only minor discrepancies between the Sponsor data listings and source documents were noted and the inspector thought these would not significantly impact the NDA analyses. Adverse events were accurately reported with the exception of one (a headache) that was reported late. The conclusion of the OSI inspection was, “In general, this study appears to have been conducted adequately and the data in support of the NDA appear reliable. The final classification at the UCSF site was No Action Indicated (NAI), and although a few minor discrepancies were found, the efficacy and safety data for this Actual Use Study are considered reliable.”

12. Labeling

FDA reviewed all of the labeling submitted by the sponsor for the retail trade carton, clinic carton, consumer information leaflet, 1-count immediate container (blister), and packaging tray. Teva revised the labeling in accordance with the FDA recommendations and the

reviewers found the labeling, as revised, acceptable for approval. I agree with their assessment. (Refer to the reviews by Ysern and Rogers.)

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

NDA 21-998/S002, Plan B® One-Step, should be approved OTC for women younger than 17 years of age with the agreed upon OTC Label and Consumer Information Leaflet as negotiated between DNCE and Duramed.

- Risk Benefit Assessment

Plan B® One-Step is to be taken as a single tablet as soon as possible within 72 hours of unprotected sexual intercourse to reduce the chance of pregnancy. It has been available OTC for women 17 years of age and older since 2009 and by prescription for those less than 17 years of age since 2009. With this efficacy supplement, Teva has sought to expand the OTC population for women less than 17 years of age. I agree with the medical review team (Drs. Chang, Furlong, Mathis) that the data reviewed for this application have demonstrated that levonorgestrel 1.5 mg is a safe and effective emergency contraceptive for use by adolescents less than 17 years old without the intervention of a healthcare provider. No new safety signals have emerged since the nonprescription (and prescription) approvals of Plan B® One-Step or of Plan B® to challenge that levonorgestrel 1.5 mg is an EC with a favorable benefit/risk ratio.

There is no disagreement among the FDA physicians who are familiar with the data provided and reviewed that Plan B® One-Step meets the regulatory standards of a nonprescription drug and should be approved as such without age restriction. The Code of Federal Regulations 21 CFR 310.200 states:

“Any drug limited to prescription use under section 503(b)(1)(B) of the act shall be exempted from prescription-dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of the public health by reason of the drug’s toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and he finds that the drug is safe and effective for use in self-medication as directed in proposed labeling.”

Therefore, for a drug to be OTC, the labeling must convey the information needed to use the product safely and effectively in the absence of a healthcare practitioner. Reliance upon the product label to result in appropriate use is consistent with the tenet that the Agency has applied in the past and continues to apply when determining whether or not a product can be over-the-counter. It is an approach consistent with the regulations.

The label comprehension data confirm that women < 17 years of age comprehend what Plan B® One-Step is for and how to take it, based solely upon the product labeling. The actual use study data demonstrate that adolescents can appropriately self-select to use Plan B® One-Step based upon their own medical circumstances and that they take the medication properly

without healthcare provider intervention. The ability to do this is consistent with safe and effective use. Thus, I conclude that healthcare provider involvement is not necessary for proper use by Plan B® One-Step for any population of women who could become pregnant after unprotected sexual intercourse. By virtue of the data submitted by Teva in NDA 21-998 S002, Plan B® One-Step meets the requirements of the codified statute for an OTC drug (21 CFR 310.200) for adolescent females.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None. The CARE_{SM} Program will no longer be needed or relevant for Plan B® One-Step if the product is approved OTC without an age restriction.

- Recommendation for other Postmarketing Requirements and Commitments

None.

References:

1. Wilcox AF, Weinberg CR, O'Connor JF, et al: Incidence of early loss of pregnancy. N Engl J Med 1988;319(4):189 - 94.
2. Int J Gynaecol Obstet. 2003;82(1):127-35. ACOG Practice Bulletin, Number 43, Management of Preterm Labor. May 2003.
3. Jueckstock JK, Kaestner R, Mylonas I: Managing hyperemesis gravidarum: a multimodal challenge. BMC Med 2010;8:46
4. Klebanoff, MA, Koslowe PA, Kaslow R, et.al: Epidemiology of Vomiting in Early Pregnancy. Obstet Gynecol 1985;66(5):612-616.
5. Monsour GM, Nashaat EH: Role of Helicobacter pylori in the pathogenesis of hyperemesis gravidarum. Arch Gynecol Obstet 2011;284(4):843-7.

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/s/

ANDREA LEONARD SEGAL
11/30/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021998/S-002

OFFICER/EMPLOYEE LIST

Officer / Employee List
NDA 21998 S-002
Plan B One-Step (levonorgestrel) tablet, 1.5 mg

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list.

Doris Bates
Christina Chang
Shaw Chen
Dan Davis
Lesley Furlong
Charles Ganley
Rima Izem
Pam Lucarelli
Jennifer Mercier
Oluwamurewa Oguntimein
Lisa Soule
Susan Thompson
Yan Wang

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021998/S-002

OFFICE DIRECTOR MEMO

DIVISION DIRECTOR'S REVIEW
Division of Nonprescription Clinical Evaluation (DNCE)

Date	April 30, 2013
From	Shaw T. Chen, MD, Ph D. Acting Director, DNCE
Subject	Review of NDA supplements/amendments
NDA# /Supplement#	21-998/S-002 Class 2 Resubmission
Applicant	Teva Women's Health, Inc.
Dates of Submission of Applicant's Response¹ to FDA's CR¹ and PDUFA Goal Date	Mar 9, 2012 and Sep 9, 2012
Date of Last Addendum submitted to the Applicant's Response	Mar 13, 2013
Proprietary Name/Established (USAN) names	Plan B One-Step/levonorgestrel
Dosage forms / Strength	Tablet/1.5 mg
Proposed Indication(s)	For women to reduce chance of pregnancy after unprotected sex (if a contraceptive failed or if no birth control was used)
Recommended Action:	Approval

INTRODUCTION

This is the Division Director's review of the applicant's initial submission of March 9, 2012, and the subsequent amendments up to April 15, 2013, in response to the CR letter of December 7, 2011 issued by FDA for this NDA supplement. The original supplement, dated February 7, 2011, requested the marketing of Plan B One-Step (PBOS) be changed from dual marketing (Rx for those less than 17 years of age and OTC for purchasers 17 years and older) to an OTC product for all females of child-bearing potential. The CR letter was issued at the direction of the Secretary of HHS because she determined that the submitted data were "inadequate ... to establish that prescription dispensing requirements should be eliminated for all ages." In a memorandum to the FDA Commissioner, the Secretary noted that the original supplement did not include "data on all ages for which the drug would be approved and available OTC."

The applicant's Response submitted on March 9, 2012 and related amendments propose changes to the labeling to allow the OTC marketing of this product for use by females ages 15 years and older.² The proposed label also contains language to enforce the age limit by requiring verification of a purchaser's age prior to sale, similar to the measures restricting sales of other products to minors (e.g., nicotine replacement therapy drug products, tobacco, and alcohol).

In the Response and subsequent amendments of 2012, the applicant did not present any new clinical study or consumer behavior data. Three periodic adverse drug event reports were reviewed and an interval literature search was conducted by the primary medical reviewer in 2012.

¹ In this review, "Complete Response" or CR refers to the regulatory action issued by the FDA on Dec. 7, 2011. The applicant's initial response of 3/9/2012 to that CR is referred to as "the Response" in this memo.

² In the initial Response of March 2012, the applicant did not propose that the product be labeled or marketed as a prescription drug for females less than 15 years of age.

In the most recent amendments of March 13 and April 15, 2013, the applicant again submitted no new clinical data or labeling revisions, nor any changes to the core proposal submitted in the initial Response of 2012. Instead, the applicant proposes - as “clarifying information” or “modifications” to the earlier marketing plan - a new tertiary packaging, an educational campaign, a postmarketing monitoring program, and a willingness to consider submitting prescription (Rx) labeling for PBOS to be marketed in adolescents aged 14 years and younger.

The following information was reviewed for this memo:

- The Response by the applicant to the CR, March 9, 2012
- Primary and Secondary reviews of May, 2012 by the medical officer (Dr. Christina Chang) and the medical team leader (Dr. Lesley Furlong), respectively
- Amendments to the supplement and the Response from the applicant, June 11 & 27, 2012
- Dr. Charles Ganley’s Office Director’s Memo of September 5, 2012³
- Amendments to the supplement and the Response from the applicant, submitted March 13 and April 15, 2013
- Dr. Chang’s and Dr. Furlong’s amendments of April 5, 2013 to their reviews, addressing the applicant’s submissions up to March 13, 2013⁴.
- Labeling reviews (dated from Sept 29, 2011 to April 30, 2013) by Ms. Maria Ysern.

REGULATORY HISTORY

Dr. Christina Chang's primary clinical review and amendment provide a comprehensive summary of the regulatory history of the application that will not be re-stated in this memo.

EFFICACY AND SAFETY

The applicant has not presented any new efficacy data since the submission of the Response in March 2012; thus, no further comment on the effectiveness of the product is necessary.

The safety experience of PBOS has been updated by the applicant with 2 periodic safety reports⁵ in 2012, covering from 1/1/2011 to 3/31/2012, and 4/1/12 to 6/30/12, respectively. Dr. Chang concluded in her review of these safety reports that no new safety signals have emerged to impact on the approvability of the drug for OTC use. She provided a detailed discussion of

³ This Division Director’s Review is adapted and updated from the memo filed in DARRTS by Dr. Charles Ganley, Director, Office of Drug Evaluation IV (ODE-IV), dated 9/5/12, addressing the applicant’s Response of March 2012 and amendments of June 11 & 27 of 2012. While the final agreed-upon labeling on the product box is slightly different from his recommendation, we have arrived at the same conclusion and recommendation for approval. Information and discussion included in his memo are reiterated in this review only when necessary to avoid breaks in chain of thoughts and to make reading easier.

⁴ The applicant’s April 15 amendment on the final labeling was reviewed by Ms Ysern (no medical review needed).

⁵ Since the original approval of PBOS, a total of 12 quarterly Periodic Adverse Drug Experience Reports (PADERS), containing data through June 30, 2012, have been submitted to FDA. Review of data contained in these PADERS has not identified any new safety issue. See Medical Officer Reviews for NDA 21-998, dated May 20, 2012 and September 4, 2012.

two serious adverse events that involved a patient who developed a deep vein thrombosis (DVT) and a patient who suffered a cerebral vascular accident (CVA). She concluded that these cases were unlikely related to levonorgestrel, as also described and commented on by Dr. Ganley (see p. 2 of his memo). I agree with Dr. Chang and Dr. Ganley that the safety profile of levonorgestrel has not changed since the original NDA submission.

AVAILABILITY OF PBOS OTC

Restriction by Age

To address the HHS Secretary's concern, the applicant proposed to restrict the OTC marketing to age 15 and above.

The proposed label in the 2012 Response submission and later amendments requires proof of age before purchase. The applicant has proposed a point-of-sale restriction that prompts the cashier to verify the purchaser's age with government issued identification at the check out counter, when the product's UPC code is scanned. The applicant plans to limit the distribution to retail outlets that have a pharmacy with equipment to scan the UPC product code at the point of purchase.

The applicant explained the mechanics of this plan in their amendment of 6/27/2012:

- The age verification system at retail establishments that the applicant proposed for this product is, in general, consistent with federal and state guidelines for the sale of tobacco and alcohol.
- To verify age, the applicant has proposed that a government issued ID (e.g., driver's license, passport, military ID, immigration card) be presented to purchase the product. These types of government issued IDs contain both picture identification and a birth date. The applicant's submission noted that in some areas a state university issued ID could be used to purchase the product.
- As explained by Teva, the current retail point-of-sale system stops any transaction that requires age verification when the UPC is scanned at the checkout counter and prompts the clerk to verify age before selling the product.

To further strengthen their proposal of age restriction, the applicant makes the following statements in the most recent amendment of 3/13/2013:

- PBOS will only be available at retail outlets with an on-site pharmacy. Therefore, the product will not be sold in convenience stores or gas stations.
- The product will be placed at the Family Planning or Female Health aisles in these outlets.
- Teva will contract only with retailers willing to adhere to these limitations.
- Teva will perform a third party audit of retail outlets to assess compliance with the age-verification requirements
- PBOS will be placed in a new packaging to dissuade theft, thus also deterring under age use (see Dr. Chang's amendment to her review of the Response for detail description of the new packaging).

The post-approval education and monitoring measures described in the same amendment may also help, but will likely have limited additional effect (see Dr. Chang's amended review for details).

Effectiveness of the Age Restriction

The effectiveness of age verification in preventing sales to under age girls was documented in a 2007 publication⁶ provided by the applicant in the amendment of 6/11/2012. Of 445 purchase attempts by under age shoppers, 14 sales (3%) of Plan B were made to shoppers less than 18 years of age. In 8 of the 14 cases, the person selling the product did not ask the age of the purchaser. Compliance by pharmacies was higher among the chain pharmacies surveyed (99.7% compliance) than among non-chain, local pharmacies (91.4%). The current retail point-of-sale restriction seems to provide adequate assurance that age would be verified when necessary, a practice consistent with the age verification for other OTC products.

With the above mechanism to restrict the sale of PBOS to age 15 and older, the applicant requests that the CARE program⁷ be discontinued because they believe it would no longer be relevant to a product regulated solely as an OTC product. The medical review team and I have no objections to discontinuing the CARE program at this time if the current supplement is approved. The applicant is utilizing a system that is already in place to check the ages of purchasers of several other products that have age restrictions for the sale. Nicotine replacement products for smoking cessation have similar labeling with regard to age verification, and we currently do not require any type of evaluation of the age verification process.

While the age verification may help prevent use of PBOS by under age consumers, access to the OTC product by the 15 years old may also be impeded by the same measure as the youngest group usually do not possess any government issued pictured ID cards (before vehicle driving age, non-immigrant, etc.). It is suggested, but not required, that proof of age be extended to include documents issued by other credible, established public/private institutions.

Prescription Availability of PBOS for Consumers Under Age 15

In the earlier application to seek OTC approval for all ages (the Response of 2012), the applicant did not consider it necessary to maintain the prescription labeling for consumers under 15 years of age. With the current proposed labeling prohibiting sale of PBOS to consumers under 15 years of age, such consumers will need to rely on other options to obtain emergency contraception.⁸ To mitigate this situation and maintain access to PBOS by this age group, Teva stated in the amendment of 3/13/2013 it would consider submitting a separate supplement to the Division of Reproductive and Urologic Products (DRUP), within 90 days of the OTC approval, for a prescription product for adolescents under 15 years of age. Their plan for a submission to maintain Rx access to adolescents under 15 seems appropriate. Generic versions of Plan B are currently available by prescription to adolescents under 17 years of age.

LABELING

There are several labeling changes proposed by the applicant in the Response and subsequent amendments that are outlined in the following table (from Dr. Ganley's memo).

⁶ "Plan B as a Dual Label Product. One-Year Update", Corrado JA, Stiffel P, Walsh M, Hummel A., U.S. Pharmacist December 2007. www.uspharmacist.com.

⁷ The Convenient Access Responsible Education (CARE) program was implemented to insure that the dual marketing (prescription/OTC) status of Plan B was followed. The components included labeling/packaging, education, distribution and monitoring of compliance with the prescription dispensing requirements.

⁸ Generic levonorgestrel in two .75 mg doses and ulipristal acetate 30 mg are available as prescription alternatives to PBOS.

Labeling of currently marketed product	Revised Labeling Proposed by the Applicant in the Response to CR
	Language added to the principal display panel in the original supplement: (b) (4) Revised language included in the submission: (b) (4)
	A box has been added on the back carton panel that includes the following bullets: <ul style="list-style-type: none"> • Not for sale to those under 15 years of age • Proof of age required • Not for sale where age cannot be verified.
In the Use section: "reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)"	In the Use section: "for women to reduce chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)"
Under the <i>Directions</i> section, the first bulleted statement: "women 17 years of age or older"	Under the <i>Directions</i> section, the first bulleted statement: (b) (4)
Under the <i>Directions</i> section, the second major bulleted statement: "prescription only for women younger than age 17. If you are younger than age 17, see a healthcare professional"	This bullet is deleted.
	Added to the consumer information leaflet: If you are sexually active, you should see a healthcare provider for routine checkups. Your healthcare provider will talk to you about and, if necessary, test you for sexually transmitted diseases, teach you about effective methods of routine birth control, and answer any other questions you may have.

The proposed change to the language of the Use section is acceptable, as are the elimination of the second bullet in the directions section and the addition to the consumer information leaflet. The other three changes to the label were discussed with the applicant in a meeting on April 10, 2013. Agreement was reached on the following:

First, in the original supplement, the applicant requested that the principal display panel include the following language, (b) (4) In the current submission, the

applicant proposed to revise the language to [REDACTED] (b) (4)

[REDACTED] should be changed to “For age 15 and older” on the principal display panel.

Second, the applicant requests that the following information be included on the back panel outside of the drug facts box.

- Not for sale to those under 15 years of age
- Proof of age be required
- Not for sale where age cannot be verified

At the meeting of 4/10/2013, FDA noted that similar information is on the back panel of OTC nicotine products and agreed with this request.

Third, under the directions section, the applicant proposed removing the statement "women 17 years of age or older." Without this sentence, the label no longer indicates the intended population for the product. The applicant should keep the statement but change it to "women 15 years of age or older." In addition, this should appear as the first bullet. The first bullet should read, “women 15 years of age or older, take as soon as possible within 72 hours (3 days) after unprotected sex. The sooner you take it the better it will work.”

Fourth, under the directions section, the bullet “[REDACTED] (b) (4) [REDACTED] should be moved to the second bullet and re-worded as [REDACTED] (b) (4) [REDACTED] There are prescription emergency contraception options available to a female less than 15 years of age that can be discussed with the doctor.

Fifth, the word “New!” located in the upper right corner on the product identification card (which is to be inserted into the clamshell package) should be revised to “New! Now available over the counter”, to qualify with what is new for clarity. The “New!” banner should be removed after six months of marketing.

The final labeling language regarding the above issues was submitted by the applicant in an amendment of April 15, 2013, which was accepted by the FDA labeling review team.

DISCUSSION

The applicant has provided a plan for the sale of PBOS utilizing current processes that restrict the sale of other age-sensitive products such as nicotine replacement products for smoking cessation and alcohol. The applicant has explained that it only plans to distribute the product to retail outlets with a pharmacy and that agree to limit the OTC sale to purchasers 15 years of age and older. Dr. Chang and Dr. Furlong in their reviews state that they still believe that the product can be sold OTC without any restriction based on age, as do I and Dr. Ganley. While Dr. Furlong believes that the current submission should not be approved because she believes that no age restrictions are necessary, I agree with Dr. Chang and Dr. Ganley that the current application should be approved. The applicant's original supplement requesting OTC availability without age restriction received a complete response letter stating that the data in the

supplement were inadequate to support approval. In the current submission, the applicant chose not to further supplement with new data or statistical analyses, but rather to seek OTC approval for females 15 and over. Recent amendments to the applicant's Response have proposed minor modifications of this original plan, which have not altered the benefit/risk assessment regarding OTC marketing of PBOS. I believe that the applicant has submitted adequate data to support OTC use by females ages 15 and older.

CONCLUSION

- The program proposed by the applicant to limit the sale of the product to purchasers age 15 and older and to verify the age of the purchaser is acceptable.
- Prescription emergency contraceptives will continue to be available to females less than 15 years of age after discussion with a health provider.
- The labeling that includes the following language is acceptable:
 - Under the Directions section, add a new first bullet, starting with the text "women 15 years of age and older" and continuing with "take as soon as possible within 72 hours (3 days) after unprotected sex. The sooner you take it the better it will work." (text previously proposed as the second bullet).
 - Under the Directions section, in what was proposed as the first bullet but now would be the second bullet, say "women under 15 years of age: talk to a doctor." instead of (b) (4)
 - The third bullet will still read: "if you vomit within 2 hours after taking the medication, call a healthcare professional to find out if you should repeat the dose."
 - The following bullets should be displayed on the back panel outside of the drug facts box as proposed by the applicant:
 - Not for sale to those under 15 years of age
 - Proof of age required
 - Not for sale where age cannot be verified
- The following language on the principal display panel should be changed from (b) (4) and older" to "For age 15 and older."
- The "New!" banner should be revised to "New! Now available over the counter".
- Other labeling recommendations in the labeling review are acceptable.
- The CARE program can be discontinued.

RECOMMENDATION

Approval.

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/s/

SHAW T CHEN
04/30/2013

Office Director Memo

Date	September 5, 2012
From	Charles J. Ganley, M.D. <i>Charles J. Ganley</i> 9/5/12
NDA/BLA # Supplement #	21-998/ S-002/Resubmission Class 2
Applicant	Teva Women's Health, Inc.
Date of Submission	March 9, 2012
PDUFA Goal Date	September 9, 2012
Proprietary Name / Established (USAN) Name	Plan B One-Step® / Levonorgestrel
Dosage Forms / Strength	Tablet / 1.5 mg
Proposed Indication(s)	For women to reduce chance of pregnancy after unprotected sex (if a contraceptive failed or if the woman did not use birth control)
Recommended Action:	Approval

Introduction

The sponsor submitted a response to the December 7, 2011 complete response letter for this NDA supplement. The original supplement, dated February 7, 2011, requested the marketing of Plan B One-Step be changed from dual marketing (Rx for those less than 17 years of age and OTC for purchasers 17 years and older) to an OTC product for all females of child-bearing potential. The complete response letter was issued at the direction of the Secretary of HHS because she determined that the submitted data were "inadequate . . . to establish that prescription dispensing requirements should be eliminated for all ages." In a memorandum to the FDA Commissioner, the Secretary noted that the original supplement did not include "data on all ages for which the drug would be approved and available OTC."

This current submission, dated March 9, 2012, proposes changes to the labeling so that the product would be indicated for use only by females ages 15 years and older. The sponsor does not propose that the product be labeled or marketed as a prescription drug for females less than 15 years of age. The proposed label also contains language to restrict sale of the product to those 15 and older and require verification of a purchaser's age prior to sale. The age of the purchaser would be checked at the cash register, not unlike what is done when other products with age restrictions are purchased in various types of retail outlets (e.g., nicotine replacement therapy drug products, tobacco, alcohol).

There were no new clinical data or consumer behavior data provided in this submission. Three periodic adverse drug event reports were reviewed and an interval literature search was conducted by the primary medical reviewer.

The following information was reviewed for this memo:

- March 9, 2012 complete response submission
- June 11, 2012 amendment to the supplement
- June 27, 2012 amendment to the supplement
- Memos by the medical officer (Dr. Christina Chang), the medical team leader (Dr. Lesley Furlong) and the labeling reviewer (Ms. Maria Ysern).

Regulatory History

Dr. Christina Chang's (primary medical officer) review provides a comprehensive summary of the regulatory history of the application that will not be re-stated in this memo.

Safety

Dr. Chang conducted a comprehensive review of the periodic safety reports submitted to the application covering a period of April 1, 2011 to March 31, 2012. She concluded that there were no new

safety signals that would impact on the safety of the drug for OTC use. She provided a detailed discussion of two serious adverse event reports that involved a patient who developed a deep vein thrombosis (DVT) and a patient who suffered a cerebral vascular accident (CVA). She concluded that these cases were unlikely related to levonorgestrel. In the case of the patient who developed a DVT, the 22 year old woman was an art student who kept her arm in a forced fixed position for several hours each day and developed a DVT in her arm. Dr. Chang observed that the additional data that would be needed as part of this patient's work-up to exclude other causes for DVT were not obtained. In the case of the patient who suffered a CVA, the 23 year old woman had a history of migraine and a significant family history of CVA, including a CVA in her mother at age 45. The stroke case appears to be the first case of stroke associated with progestin only emergency contraceptive reported in the literature. Dr. Chang concluded that it is unlikely this case was related to a single dose of a progestin oral contraceptive. Additionally, she notes that third generation progestins, such as drospirenone, may confer a greater risk for thrombosis in combination oral contraceptives compared to second generation progestin combination oral contraceptives. The epidemiologic investigation that suggested an increased risk for third generation progestins did not implicate an increased risk for progestin-only oral contraceptives. I agree with Dr. Chang that it is difficult to implicate a causal role for levonorgestrel in either of these cases.

An additional periodic safety report was submitted during the review of this supplement that covered the period of 4/1/12 to 6/30/12. Dr. Chang assessed the report and concluded that no new safety signals are identified. I agree with Dr. Chang's interpretation of this report.

Amendments to Supplement

The proposed label in the current submission requires proof of age before purchase. The sponsor has proposed a point of sale restriction that prompts the cashier to verify the purchaser's age with government issued identification at the point of sale, when the product's UPC code is scanned. The sponsor plans to limit the distribution to retail outlets that have a pharmacy and where the UPC product code will be scanned at the point of purchase. If, despite these point-of-sale restrictions, an underage sale were to occur, I do not believe that the risk presented by this potential negates my determination that this product as proposed in this submission (with labeling modifications described below) is safe and effective as an OTC drug.

On June 27, 2012, the sponsor provided an amendment that further explained their plans to limit the sale of the product to purchasers ages 15 and older, including information about the type of identification that the retailers would use to verify proof of age.

- The age verification system at retail establishments that the sponsor described for this product is generally consistent with federal and state guidelines for the sale of tobacco and alcohol.
- To verify age, the sponsor has proposed that a government issued ID (e.g., driver's license, passport, military ID, immigration card) be presented to purchase the product. These types of government issued IDs contain both picture identification and a birthdate. The sponsor's submission noted that in some areas a state university issued ID could be used to purchase the product.
- As explained by Teva, the current retail point-of-sale system stops any transaction that requires age verification when the UPC is scanned and prompts the clerk to verify age before selling the product.

On June 11, 2012, the sponsor provided information regarding 14 sales of Plan B that were made to shoppers less than 18 years of age out of 445 purchase attempts by underage shoppers as reported in a 2007 publication "Plan B as a Dual Label Product One Year Update".¹ This information was collected as

¹ This is an article that appeared in U.S. Pharmacist, December 2007. The authors are employees of Duramed Research, Inc. and Barr Laboratories, Inc. U.S. Pharmacist is a monthly journal dedicated to providing the nation's pharmacists with up-to-date, authoritative, peer-reviewed clinical articles relevant to contemporary pharmacy practice in a variety of settings, including community pharmacy, hospitals, managed care systems, ambulatory care

part of the CARE program². Information was available for further assessment for 8 of the 14 cases. In these 8 cases, the person selling the product did not ask the age of the purchaser. As discussed further below, I believe the current retail point of sale restriction would provide adequate assurance that age would be verified when necessary, consistent with the age verification for other OTC products.

Availability of Plan B One-Step in someone younger than 15 years of age

The sponsor did not propose to maintain the prescription labeling for persons under 15 years of age. The labeling on the proposed carton includes the following in the directions section of the Drug Facts labeling: (b) (4)³ Outside of the Drug Facts box, the following labeling statement is included: "Not for sale to those under 15 years of age." Even with the proposed labeling prohibition for sale of Plan B One-Step to consumers under 15 years of age, there remain prescription options available to someone under 15 years of age to obtain emergency contraception.

- Generic levonorgestrel in two .75 mg doses and ulipristal acetate 30 mg are available as prescription alternatives to Plan B One-Step. Under the proposed OTC marketing for Plan B One-Step, someone under 15 years of age could visit a physician or other appropriate health provider and have a prescription written for one of these emergency contraceptive products.

Labeling

There are several labeling changes proposed by the sponsor that are outlined in this table.

Current Labeling	Revised Labeling Proposed in this Submission
	Language added to the principal display panel in the original supplement: (b) (4) Revised language included in this submission: (b) (4)
	A box has been added on the back carton panel that includes the following bullets: <ul style="list-style-type: none"> Not for sale to those under 15 years of age Proof of age required Not for sale where age cannot be verified.
In the Use section: "reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)"	In the Use section: "for women to reduce chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)"
Under the <i>Directions</i> section, the first bulleted statement: "women 17 years of age or older"	Under the <i>Directions</i> section, the first bulleted statement: (b) (4)

clinics, home care organizations, long-term care facilities, industry and academia (from <http://www.uspharmacist.com/>).

² The Convenient Access Responsible Education program was implemented to insure that the dual marketing (prescription/OTC) status of Plan B was followed. The components included labeling/packaging, education, distribution and monitoring of compliance with the prescription dispensing requirements.

³ I recommend a modification to this language below.

Current Labeling	Revised Labeling Proposed in this Submission
<p>Under the <i>Directions</i> section, the second major bulleted statement:</p> <p>“prescription only for women younger than age 17. If you are younger than age 17, see a healthcare professional”</p>	<p>This bullet is deleted.</p>
	<p>Added to the consumer information leaflet:</p> <p>If you are sexually active, you should see a healthcare provider for routine checkups. Your healthcare provider will talk to you about and, if necessary, test you for sexually transmitted diseases, teach you about effective methods of routine birth control, and answer any other questions you may have.</p>

The proposed change to the language of the Use section is acceptable. The elimination of the second bullet in the directions section is acceptable. The addition to the consumer information leaflet is acceptable. The other three changes to the label warrant further discussion.

First, in the original supplement, the sponsor requested that the principal display panel include the following language, (b) (4). In this submission, the sponsor proposed to revise the language to, (b) (4). The labeling reviewer found this language to be acceptable.

(b) (4)

(b) (4)

(b) (4) I do not believe the inclusion of this language is necessary for the appropriate sale of the product. I recommend that it not be included on the principal display panel at all.

Second, the sponsor requests that the following information be included on the back panel outside of the drug facts box.

- Not for sale to those under 15 years of age
- Proof of age be required
- Not for sale where age cannot be verified

These three bullets should be placed on the principal display panel so they are more prominently displayed. I also do not believe, as suggested in Dr. Chang’s review, that those three bullets conflict with the statement elsewhere in the labeling to contact a doctor if under age 15. The statements taken together suggest that the product is not to be sold OTC to persons under 15 and that if a female is under 15, she should consult her doctor to discuss her use of an emergency contraceptive product.

Third, under the directions section, the sponsor proposed removing the statement “women 17 years of age or older”. Without this sentence, the product no longer indicates the intended population for the product. I propose that the sponsor keep the statement but change it to (b) (4).

Fourth, the sponsor proposed the following under the directions section of the labeling, (b) (4)

(b) (4)

(b) (4) There are prescription emergency contraception options available to a female less than 15 years of age, and the discussion with the doctor can include those options. I also prefer “talk with a doctor” instead of (b) (4)

Mechanisms for Checking Proof-of-Age

Teva sent in a submission dated June 27, 2012 that explained the mechanics of how they plan to limit the OTC sale of Plan B One-Step to consumers ages 15 and over. As noted in this submission (and in their March 9, 2012 submission, albeit in less detail), they plan to follow the model used for approved nicotine replacement therapy drug products that have the same language limiting sale by age, and have worked with retailers to have the products scanned at the retail sales counter. Once the UPC code is scanned, there will be a prompt on the register screen for the cashier to check the purchaser's age/birthdate. The product will not be sold to those under 15. Their proposal/explanation seems reasonable to ensure that sales of the product are limited to those 15 and older. If, despite these point-of-sale restrictions, an underage sale were to occur, I do not believe that the risk presented by this potential negates my determination that this product as proposed in this submission (with labeling modifications described below) is safe and effective as an OTC drug.

CARE Program

The sponsor requests that the CARE (Convenient Access Responsible Education) program be discontinued because they believe it would no longer be relevant to a product regulated solely as an OTC product. I have no objections to discontinuing the CARE program at this time if the current supplement is approved. The sponsor is utilizing a system that is already in place to check the ages of purchasers of products that have age restrictions for the sale of the product. Nicotine replacement products for smoking cessation have similar labeling with regard to age verification, and we currently do not require any type of evaluation of the age verification process.

Discussion

The sponsor has provided a plan for the sale of Plan B One-Step utilizing current processes that restrict the sale of other age restricted products such as nicotine replacement products for smoking cessation and alcohol. The sponsor has explained that it only plans to distribute the product to retail outlets with a pharmacy and that agree to limit the OTC sale to purchasers 15 years of age and older. Dr. Chang and Dr. Furlong in their reviews state that they still believe that the product can be sold OTC without any restriction based on age, as do I. While Dr. Furlong believes that the current submission should not be approved because she believes that no age restrictions are necessary, I agree with Dr. Chang that the current application should be approved. The sponsor's original supplement requesting OTC availability without age restriction received a complete response letter stating that the data in the supplement were inadequate to support approval. In the current submission, the sponsor chose not to further supplement with new data or statistical analyses, but rather to seek OTC approval for females 15 and over. I believe that the sponsor's current submission contains adequate data to support OTC use by females ages 15 and older.

Conclusion

- The program proposed by the sponsor to limit the sale of the product to purchasers age 15 and older and to verify the age of the purchaser is acceptable.
- Prescription emergency contraceptives will continue to be available to females less than 15 years of age after discussion with a health provider.
- The labeling that includes the following language is acceptable:
 - Under the Directions section, add a new first bullet, "women 15 years of age or older"
 - Under the Directions section, in what was proposed as the first bullet but now would be the second bullet, "If you are under 15 years of age, talk with a doctor" instead of (b) (4)
- The following bullets should be displayed on the principal display panel for more prominence instead of on the back of the carton as proposed by the sponsor.
 - Not for sale to those under 15 years of age
 - Proof of age required

- Not for sale where age cannot be verified
- Remove the following language from the principal display panel: [REDACTED] (b) (4)
- Other labeling recommendations in the labeling review are acceptable.
- The CARE program can be discontinued.

Recommendation

Approval.

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/s/

DORIS J BATES

04/30/2013

Signed in for Dr. Charles Ganley. Please see his signature and date on first page of scanned review.

Office Director Memo

Date	March 23, 2012
From	Charles J. Ganley, M.D.
Subject	Classification of Complete Response Submission
NDA #	21-998/S-002
Applicant Name	Teva Women's Health
Date of Submission	March 9, 2012
Product Name	Plan B One-Step (levonorgestrel)
Dosage Form	1.5 mg tablet
Proposed Indication	OTC Emergency Contraception

On February 11, 2011, Teva Women's Health submitted S-002 to NDA 21-998 requesting a switch of Plan B One-Step to full nonprescription status. In December 2011, after completing its scientific review, FDA was prepared to approve a full OTC switch of Plan B One-Step, concluding that the sponsor's SNDA contained "adequate and reasonable, well-supported, and science-based evidence that Plan B One-Step is safe and effective and should be approved for nonprescription use for all females of childbearing potential." Statement of Dr. Margaret Hamburg, Commissioner of Food and Drugs, at 1 (Dec. 7, 2011) (<http://www.fda.gov/NewsEvents/Newsroom/ucm282805.htm>). The Secretary of Health and Human Services, however, determined that the Plan B One-Step data were insufficient, and on December 7, 2011, directed the FDA to issue a Complete Response (CR) letter to the sponsor. Memorandum from Kathleen Sebelius, Secretary of Health and Human Services, at 2 (Dec. 7, 2011) (<http://www.hhs.gov/news/press/2011pres/12/20111207a.html>). The CR letter indicated that the supplement could not be approved and was deficient because the Secretary had concluded that the data "submitted for this product are inadequate to support approval in that they do not establish that prescription dispensing requirements should be eliminated for all ages."

The CR letter described the options available to Teva, which included resubmitting the supplement and addressing all of the deficiencies listed in the CR letter within one year after the date of the letter. On March 9, 2012, Teva responded to the CR letter with a resubmission. In the resubmission, the Teva proposes the following:

- Removal of the Rx legend from the package
- Change the age for non-prescription use from 17 to 15 [REDACTED] (b) (4)
- Add a requirement that the age of the purchaser be verified by the cashier at the point of sale by incorporating a trigger based on the UPC code
- Limit distribution to retail outlets with an on-site pharmacy with product placement in the family planning aisle
- Label the product with the following information outside of the drug facts box
 - Not for sale to those under 15 years of age
 - Proof of age required
 - Not for sale where age cannot be verified

Teva requests that their resubmission in response to the CR letter be considered a Class 1 resubmission, which would qualify for a 2-month PDUFA review goal.¹ A Class 1 resubmission is defined as a resubmission that includes one or more of the following items:

1. Final printed labeling; 2. Draft labeling; 3. Safety updates submitted in the same format, including tabulations, as the original safety submission with new data and changes highlighted (except when large amounts of new information, including important new adverse experiences, not previously reported with the product are presented in the resubmission); 4. Stability updates to support provisional or final dating periods; 5. Commitments to perform mandatory postmarketing studies, including proposals for such studies; 6. Assay validation data; 7. Final release testing on the last 1-2 lots used to support approval; 8. A minor re-analysis of data previously submitted to the application (determined by the FDA as fitting the Class 1 category); 9. Other minor clarifying information (determined by the FDA as fitting the Class 1 category).²

A resubmission that is not considered a Class I resubmission is considered a Class 2 resubmission with a 6-month PDUFA goal date.³

Teva does not explain their rationale for requesting that their resubmission be classified as Class 1, and I have determined that this resubmission is not “minor” in nature and should be classified as a Class 2 resubmission for the reasons described below.

The paradigm proposed by Teva represents a significant change from what was proposed in the original efficacy supplement for full OTC switch of Plan B One-Step. That proposal did not include any requirement for age verification or restriction of sales and provided for access to the product to women of all ages in need of emergency contraception. The changes proposed will require consideration of new carton and container labeling, with new language concerning the age restriction and the point of sale verification of that restriction. In addition, although Teva cites the precedent of the age restriction for OTC sale of some nicotine replacement therapy products, with this submission, FDA will need to assess *requiring* as a condition of approval of an OTC product that sales be restricted to a certain age group. These are not the types of minor issues that were envisioned when the Class 1 resubmission category for PDUFA performance goals was developed. Review of the resubmission will require a considerable effort on the part of FDA and is consistent with the more extensive review expected under the PDUFA goals for a Class 2 resubmission. Therefore, I conclude that the resubmission should be classified as Class 2 with a 6-month PDUFA goal for review.

Charles J. Ganley, M.D.
Director, ODEIV

¹ 21 CFR 314.110(b).

² 21 CFR 314.3; FDA CDER MAPP 6020.4; see also Guidance for Industry, “Classifying Resubmissions in Response to Action Letters” April 1998.

³ 21 CFR 314.110(b).

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/s/

CHARLES J GANLEY
03/23/2012



FROM: Margaret A. Hamburg, M.D., Commissioner

TO: Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research

RE: NDA 21-998/Supplement-002

DATE: December 7, 2011

As you know, I have been considering the determination of the Center for Drug Evaluation and Research (CDER) that the Plan B One Step supplement for non-prescription use to reduce the chance of pregnancy after unprotected sex for all women of child-bearing potential should be approved. I reviewed and considered data, information, and analysis provided by CDER, and concluded that the center has identified reasonable and well-supported bases for its scientific determination that levonorgestrel 1.5 mg tablet (Plan B One-Step) is safe and effective for non-prescription use to reduce the chance of pregnancy after unprotected sex for all women of child-bearing potential. I conveyed my support for approval of this application to you by telephone yesterday.

Yesterday afternoon I was informed that on December 7, 2011, the Secretary of Health and Human Services would issue a memorandum to FDA stating that she had considered a CDER review document for this application and concluded that the data are inadequate to support approval for all ages. The memorandum would direct the agency to issue a complete response letter to the sponsor citing inadequate data to support nonprescription use for all ages.

I have now received the attached Memorandum. The Secretary's stated views are contrary to my conclusions and to those of CDER, which found, among other things, that the data submitted for this application have demonstrated that levonorgestrel 1.5 mg is a safe and effective emergency contraceptive for use by adolescents less than 17 years old without the intervention of a healthcare provider. CDER also found that no new safety signals have emerged since the nonprescription (and prescription) approvals of Plan B One-Step and of Plan B® to challenge that levonorgestrel 1.5 mg is an emergency contraceptive with a favorable benefit/risk assessment.

The Secretary has directed the agency to issue a complete response letter to the sponsor that represents her view as described in the Memorandum.


Attachment



THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

MEMORANDUM

TO: Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

FROM: Kathleen Sebelius 

SUBJECT: Supplemental New Drug Application (NDA 21-998/S002)

DATE: December 7, 2011

On February 7, 2011, Teva Women's Health Inc. submitted to the Food and Drug Administration (FDA) a supplemental new drug application (NDA 21-998/S002) for Plan B One-Step (levonorgestrel 1.5 mg), an emergency contraceptive that can prevent pregnancy if taken within 72 hours of sexual intercourse. The application seeks FDA approval to market Plan B One-Step as a non-prescription drug product without any age restriction. Currently, this drug product, like other FDA-approved (levonorgestrel) emergency contraception drug products, is sold exclusively from behind the pharmacy counter and is available without a prescription only for women ages 17 years and older; women 16 and younger can obtain this drug product only by prescription.

I have carefully considered FDA's Division Director Summary Review of Regulatory Action, dated November 30, 2011, for the supplemental application, which represents the position of the FDA and recommended approval of the application. Based on my review, I have concluded that the data submitted for this product do not establish that prescription dispensing requirements should be eliminated for all ages.¹

The label comprehension and actual use studies submitted to FDA do not include data on all ages for which the drug would be approved and available over-the-counter. Yet, it is commonly understood that there are significant cognitive and behavioral differences between older adolescent girls and the youngest girls of reproductive age, which I believe are relevant to making this determination as to non-prescription availability of this product for all ages. Although the average age of the onset of menses for girls in the United States is 12.4 years of age, about ten percent of girls reach menarche by 11.1 years of age.² If the application is approved, the product would be available, without a prescription or other point-of-sale restrictions, even to the youngest girls of reproductive age.

¹ See 21 C.F.R. § 310.200(b).

² Chumlea WC, Schubert CM, Roche AF, Kulin HE, Lee PA, Himes JH, Sun SS: Age at Menarche and Racial Comparisons in U.S. Girls. *Pediatrics* 2003;111(1): 110-113.

The Federal Food, Drug, and Cosmetic Act provides that “[t]he Secretary [of Health and Human Services], through the Commissioner, shall be responsible for executing” its provisions.³ As such, I direct FDA to issue a complete response letter because the data submitted for this product are inadequate to support approval in that they do not establish that prescription dispensing requirements should be eliminated for all ages.

³ 21 U.S.C. § 393(d)(2).

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/s/

GERALDINE N SMITH
12/07/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021998/S-002

CROSS DISCIPLINE TEAM LEADER REVIEW

Addendum to Cross-Discipline Team Leader Review

Date	19-Mar-2012
From	Lesley-Anne Furlong, MD, Division of Nonprescription Clinical Evaluation
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	21-998
Supplement#	
Applicant	Teva Women's Health, Inc.
Date of Submission of Complete Response	9-Mar-2012
PDUFA Goal Date	9-Sep-2012
Date of Amendment	13-Mar-2013
Proprietary Name / Established (USAN) names	Plan B One-Step/levonorgestrel
Dosage forms / Strength	Tablet/1.5 mg
Proposed Indication(s)	For women to reduce chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)
Recommended:	Complete Response

1. Introduction

This is a review of an amendment to a supplemental submission by Teva Women's Health (Teva) addressing FDA's Complete Response letter dated 7-Dec-2011. Teva's amendment (submitted 13-Mar-2013) consists of a letter providing clarifying information, commitments, and minor changes. The amendment does not change Teva's core proposal to market Plan B One-Step as an OTC product that is restricted for sale to women 15 years of age and older.

Teva indicates in the cover letter that the proposals in the amendment were requested by the FDA. Members of the review team in the Division of Nonprescription Clinical Evaluation did not request the proposals.

The submission does not contain any new labeling or data.

2. Proposals in the Amendment

The proposals in the amendment include:

- 1) Teva commits to contract only with distributors and retailers who are willing to adhere to limiting distribution to outlets with an on-site pharmacy, and to placement in the Family Planning/Female Health aisle of those retail outlets.

Comment: The only change here is the commitment "to contract only with distributors and retailers who are willing to adhere"; this does not change my risk/benefit assessment, and it is acceptable to me.

- 2) Teva will enclose the packaged product in an over-package of heavy gauge clear plastic, known in the packaging industry as a “clamshell.”

Comment: This type of clamshell packaging is used as a theft deterrent in consumer products, including OTC drug products (e.g., Abreva). The clamshell is tertiary level packaging and will not directly contact the drug product; therefore, the clamshell does not raise product quality concerns. The clamshell makes it more difficult to access the product and makes the packaging bulkier. Opening clamshells may require scissors or a knife. As many consumer products are packaged in clamshells, consumers should be familiar with the challenges of accessing a product in clamshell packaging. The proposal does not change the risk/benefit assessment, and it is acceptable (but unnecessary) to me.

- 3) Teva commits to a marketing/educational plan and a third party audit of retail outlets.

The marketing/educational plan will inform consumers and healthcare professionals about the OTC status of Plan B One-Step, where the product may be purchased, and the age restriction/verification requirements.

The third party audit will assess compliance with age-verification at retail outlets. The audit will be a mystery shopper audit similar to the one carried out under the CARE program for Plan B and Plan B One-Step. The audit will take place six months after launch. Teva’s commitment provides for the potential for a follow-up audit approximately six months later if significant noncompliance is identified.

Comment: The elements of the marketing/educational plan provided by Teva are truthful and therefore acceptable to me. The proposal to audit compliance with age-verification does not change my risk/benefit assessment, and is also acceptable (but unnecessary) to me.

- 4) Teva anticipates submitting a supplement for a prescription version of Plan B One-Step for women under the age of 15 years within 90 days after approval of the OTC product.

Comment: The proposal may improve access for younger girls and is therefore acceptable to me. Whether or not Teva submits a supplement for a prescription product, Plan B and its generics remain available by the prescription route to women younger than 15.

3. Safety

The applicant’s most recently submitted periodic adverse drug experience report (submitted 31-Jul-2012) was reviewed by Dr. Chang on 4-Sep-2012. No new safety issues were identified. FDA does not currently have any open tracked safety issues for Plan B One-Step or Plan B.

4. Labeling

As noted in my previous review, I do not recommend labeling that makes access difficult for particular women (the youngest and those without age verification on hand) who may need postcoital contraception. Other than the age restriction, the labeling is acceptable to me.

5. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I continue to recommend a complete response action unless the proposed OTC labeling is changed to include all women of reproductive age. There is nothing in the amendment to change my previous recommendation. The changes and commitments in the amendment are unnecessary but acceptable to me.

Plan B One-Step has met the regulatory requirements for OTC marketing. Teva's current proposal of restricting sales to women who are 15 and older continues an unnecessary burden of age verification on the staff in retail outlets and young women who need the product; continues to delay access to a time-sensitive product for women who do not have proof of age on hand; and presents a road-block to teens younger than 15 years of age.

OTC labeling for all women of reproductive age would allow all women the same access to Plan B One-Step that all men have to condoms. Rapid access to Plan B One-Step matters: time is of the essence for effectiveness. Denying condoms to men who do not have proof of age on hand or who are younger than 15 would not serve the public health. Imposing these requirements on women who need Plan B One-Step does not serve the public health either.

Plan B One-Step is a low-risk, nonaddictive product with a simple label; packaging contains a single pill. The labeling compares favorably to the labeling of many OTC products, such as cough-cold products or painkillers, which have more complex dosing regimens and may be purchased in larger quantities by consumers of any age.

I agree with the primary clinical reviewer that the proposed label is likely to be an improvement over, and is no worse than, current dual labeling. Nonetheless, I am unable to recommend labeling that limits access to a safe, time-sensitive contraceptive for women who do not have proof of age on hand or who are younger than 15 years of age. I am also unable to determine whether Teva's submission fully addresses the issues raised by Secretary Sebelius in the Complete Response action of 7-Dec-2011 as the Secretary's memo did not provide guidance about data, studies, or labeling changes that she would find acceptable.

- Risk/Benefit Assessment

The amendment does not impact my previous risk/benefit assessment.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Standard postmarketing pharmacovigilance is appropriate. The proposed postapproval “Education and Monitoring” plan is unnecessary but acceptable to me.

- Recommendation for other Postmarketing Requirements and Commitments

None

- Recommended Comments to Applicant

None

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/s/

LESLEYANNE FURLONG
04/05/2013

Cross-Discipline Team Leader Review

Date	20-May-2012
From	Lesley-Anne Furlong, MD, FACOG
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	21-998
Supplement#	
Applicant	Teva Women's Health, Inc.
Date of Submission	9-Mar-2012
PDUFA Goal Date	9-Sep-2012
Proprietary Name / Established (USAN) names	Plan B One-Step/levonorgestrel
Dosage forms / Strength	Tablet/1.5 mg
Proposed Indication(s)	For women to reduce chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)
Recommended:	Complete Response

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1. Introduction

This is a summary review of a submission by Teva Women's Health (Teva) addressing FDA's Complete Response letter dated 7-Dec-2011. The submission contains a cover letter describing a new marketing proposal, new proposed labeling, and a safety update that points to three routine periodic adverse drug experience reports (PADERS) that Teva has submitted to their NDA since the last review cycle. Teva submitted a fourth PADER during the review cycle and the review team included the fourth PADER in the review.

2. Background

Plan B One-Step has a complicated regulatory history that has been summarized in numerous reviews, including my own review of the previous submission (see Appendix). The following is a summary of the interval regulatory events resulting in the present submission.

On 7-Feb-2011, Teva submitted a supplement seeking over-the-counter (OTC) labeling for all women of reproductive age for Plan B One-Step. At the time, each carton of Plan B One-Step was labeled in the United States both as a prescription product for women younger than 17 years old and as an OTC product for women 17 years and older. The dual labeling meant that Plan B One-Step was kept behind the pharmacy counter, and women in need had to interact with a pharmacist to either fill a prescription or verify they were at least 17 years old.

The 7-Feb-2011 submission contained final reports for a label comprehension study and an actual use study, a literature review, an analysis of postmarketing safety, and proposed OTC labeling for all women of reproductive age. The review team unanimously concluded that the application should be approved. The FDA's Commissioner, Dr. Margaret Hamburg, agreed with the review team in a memo dated 7-Dec-2011; however, on the same day, the Health and Human Services Secretary, Secretary Kathleen Sibelius, took the unusual step of exercising her legal authority to over-ride the recommendation of the FDA. Ms. Sibelius' memo, dated 7-Dec-2011, stated that "the data submitted for this product do not establish that prescription dispensing requirements should be eliminated for all ages." The Secretary further stated that the consumer studies did not include data on all ages for which the drug would be available OTC, and her memo indicated that her concern was for the youngest girls of reproductive age. Finally, and also on 7-Dec-2011, Dr. Janet Woodcock, Director of FDA's Center for Drug Evaluation and Research, issued a Complete Response letter informing Teva of the Secretary's decision. The Complete Response letter did not set out specifics about how to address the Secretary's concerns, and the Secretary's memo did not provide guidance about data, studies, or labeling changes that the Secretary would find acceptable.

As a result of the Secretary's decision, Plan B One-Step remains behind pharmacy counters, and women who need it must still interact with a pharmacist to fill a prescription or verify they are at least 17 years old.

In January 2012, the Pediatric Advisory Committee (PAC) met for a routine review of a number of products, including Plan B One-Step. Under the Food and Drug Administration Amendments Act, the PAC reviews a report of adverse events for the year following product labeling under the Pediatric Research Equity Act and/or the Best Pharmaceuticals for Children Act, and makes recommendations based on its review. The review of Plan B One-Step was a routine review triggered by its 2009 approval. After discussing the postmarketing data in children, the committee voted unanimously (one abstention) that Plan B One-Step could be followed with routine postmarketing surveillance. Although the committee was not asked to vote on OTC access, several members of the committee volunteered comments in their concluding remarks on Plan B One-Step, as follows:

- “The data indicate very clearly that this product is equally safe in women of all ages, and unfortunately, the requirement that it be limited to adolescents to prescription only severely limits access to a population that desperately needs it.” (Dr. Hillard, Professor of Obstetrics and Gynecology at Stanford University School of Medicine, pediatric and adolescent gynecology)
- “I would like to support the comments of Dr. Hillard.” (Dr. White, pediatric cardiologist and Director of the ethics education program at Ochsner Health System in New Orleans)
- “And I would add that, with only 15 serious events over 9 years, that safety in children is clearly shown. I would encourage the FDA in your future deliberations to not discriminate against children in their access to this.” (Dr. Wagener, Professor of Pediatrics, University of Colorado, pediatric pulmonologist)
- “I agree fully with my fellow pediatric pulmonologist, Jeff Wagener.” (Dr. Castile, pediatric pulmonologist from Nationwide Children’s Hospital in Columbus, Ohio)
- “I do want to make note that I look forward to the day that there is no discrimination and anybody, any woman who feels she needs it of any age, can get it over the counter.” (Dr. Walker, Professor of Pediatrics at the University of Washington and Chief of the Division of Adolescent Medicine)

In the current submission, Teva decided to address the Secretary’s memo by changing the proposal for OTC labeling. Rather than label for all women of reproductive age, Teva proposes an OTC label for females who are 15 years old and older. There will be no prescription label. Labeling instructs younger women to (b) (4) language that appears on numerous OTC labels and is codified in the OTC labeling regulations (21 CFR 201.66). Teva further proposes to eliminate prescription labeling so that Plan B One-Step may be kept on the shelves of retail pharmacies with other OTC products, making the product visible to consumers and eliminating the need to interact with a pharmacist to obtain it.

The other elements of Teva’s proposal include:

- Add a requirement that the age of the purchaser be verified by the cashier at the point of sale. When the UPC code is scanned by the cashier, an automatic message will appear prompting the cashier to request proof of age.
- Limit distribution to retail outlets with an on-site pharmacy with product placement in the family planning aisle
- Label the carton with the following text that is almost identical to the text that appears on nicotine replacement therapies
 - Not for sale to those under 15 years of age

- Proof of age required
 - Not for sale where age cannot be verified.
-
- All product cartons will include a security tag to prevent product theft
 - Cessation of CARE program responsibilities. The CARE program was a postmarketing study that monitored pharmacy compliance with the dual prescription/OTC labeling.

In preparing this review, I considered Teva's submission and the review of the primary medical officer. The review of the labeling team was pending at the time this review was finalized.

3. CMC/Device

Not applicable

4. Nonclinical Pharmacology/Toxicology

No applicable

5. Clinical Pharmacology/Biopharmaceutics

Not applicable

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

Not applicable

8. Safety

The interval safety evaluation did not reveal any new safety issues or safety issues that were specific to younger teens.

The primary medical reviewer, Dr. Christina Chang, performed a detailed review of the three periodic adverse event reports (PADERS) that have been submitted since Secretary Sibelius's complete response. During the review cycle, Teva submitted a fourth PADER to the NDA, as

required for routine postmarketing surveillance. Dr. Chang included this fourth PADER in her review. Only the highlights of Dr. Chang's review appear here.

Together, the four PADERS cover the twelve-month interval from 1-Apr-2011 through 31-Mar-2011. The four PADERS contain 5,958 cases reporting adverse events associated with use of Plan B One-Step or its foreign equivalent. Most cases involved menstrual irregularity, an expected and labeled event. The other commonly reported events were nausea, pelvic pain, and vomiting, all of which are expected and labeled. Forty-one cases had serious outcomes that resulted in expedited reporting to FDA's adverse event reporting system (AERS). These cases are discussed in detail in Dr. Chang's review. Most were consumer reported. The largest cluster of expedited cases (n=18) involved miscarriages, an event that is common in women of reproductive age who become pregnant; pregnancy is expected in some women who use Plan B One-Step, even when they use it correctly, and therefore reports of miscarriage are expected as well. As noted by Dr. Chang, the PADERS overall present a benign safety profile of Plan B One-Step that is consistent with the current label.

Two literature reports from Spain described thrombotic events. Because thrombotic events are serious and have not been previously reported, I have borrowed from Dr. Chang's review to describe them in more detail.

Case# 8010310: This is a literature report concerning a 22-year-old Spanish female who developed venous thrombosis three days after taking Postinor (levonorgestrel 1.5 mg tablet) for post-coital contraception. Her past medical history included epistaxis associated with taking acetaminophen. She was an art student, and her daily routine included having her arms in fixed positions several hours per day for sculptures and painting.

She presented for care with pain and inflammation in her right upper arm, lasting approximately 24 hours. Physical examination showed edema in the arm and pain on compression of her brachial musculature. A venous Doppler ultrasound revealed occlusive thrombosis; the findings were confirmed by magnetic resonance venography (MRV). She started a six-month regimen of anticoagulation; a follow-up (MRV) showed full restoration of permeability in the affected region.

Case# 8158324: This is literature report concerning a 23-year-old female from Spain who experienced a cerebrovascular accident. The patient has a medical history of migraine without aura. Her obstetrical history included seven miscarriages in the first and second trimester of pregnancy; she had one healthy child born at term. Her family history was significant for her mother having a stroke at age 45 and her sister having repeated first trimester miscarriages.

The patient took Postinor (levonorgestrel 1.5 mg tablet) on [REDACTED] (b) (6) for emergency contraception. She then experienced reduced strength and sensitivity in the right side of her body upon awakening the next morning. She was seen at an emergency room 36 hours after the onset of symptoms. A neurological examination was consistent with cerebrovascular accident. Cerebral CT and MRI showed cerebral infarction in the left anterior thalamus. A transesophageal echocardiogram was negative. Hypercoagulability work-up, including anti-phospholipid antibodies, factor V Leiden mutation, prothrombin gene mutation, protein C and

S deficiencies, was negative. No concomitant medications were reported. She recovered from these reported events on [REDACTED] (b) (6).

It is difficult to conclude that levonorgestrel was a factor in these two cases. The first subject had a deep vein thrombosis in the arm, an unusual event, and no work-up was reported for coagulopathy. The report stated that “her daily routine included having her arms in fixed positions several hours per day” – if this is accurate, prolonged immobilization is also a risk factor for thrombosis. The reported work-up for coagulopathy in the second case was incomplete, as described in Dr. Chang’s review. The positive family history and the history of pregnancy loss are risk factors for coagulopathy in her case.

Estrogens have been associated with thrombotic events, but the contribution of progestins to thrombosis is less clear. There is evidence from observational studies that certain progestins may contribute to the risk of thrombotic events. Despite its long history of human use, levonorgestrel has not been implicated as a thrombogenic progestin. As pointed out in Dr. Chang’s review, the clinical trials for levonorgestrel-only products (Plan B, Plan B One-Step, Norplant, Jadelle, and Mirena) did not reveal a thrombotic safety signal. Dr. Chang also performed a search of FDA’s adverse event reporting system (AERS) for “deep vein thrombosis” or cerebrovascular accident” and “Plan B” or “Plan B One-Step” from the time of approval of Plan B (18-Jul-1999) through 20-Apr-2012, and she identified no additional case reports. Thrombotic events have a certain baseline incidence in women of reproductive age; this incidence increases during pregnancy and the puerperium. Venous thromboembolism is reported in about 1 in 1000 pregnancies, which is four times as great as the risk in the nonpregnant population.¹ Between Jul-09 and Jan-11, approximately 3.5 million tablets of Plan B One-Step were distributed in the United States alone. Given the extensive population exposure, the expected baseline incidence, and the other risk factors in the two cases reported from Spain, I would not recommend a labeling change for Plan B One-Step based on the two reports from Spain. Routine postmarketing surveillance should continue.

Dr. Chang also performed an interval literature search for peer-reviewed articles published since October 2011. Her search focused on emergency contraceptive use in the adolescent population; she retrieved one article that published the results of the actual use study reviewed in the previous cycle. Per Dr. Chang, “the reported findings were consistent with the information provided by the applicant in the first review cycle.”

I search FDA’s electronic archive (DARRTS) on 27-Apr-2012, and found no open tracked safety issues related to levonorgestrel.

9. Advisory Committee Meeting

Not applicable

¹ Marik PE, Plante LA. Venous thromboembolic disease and pregnancy. (2008) N Engl J Med 2008; 359:2025-2033

10. Pediatrics

The application did not trigger the Pediatric Research Equity Act because it did not propose a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

11. Other Relevant Regulatory Issues

Teva requested that the submission be considered a Class 1 resubmission, which would qualify it for a 2-month review goal. However, FDA classified the submission as a Class 2 resubmission, with a 6-month review goal, because Teva proposed a significant change from the original proposal by restricting OTC labeling and sales to women 15 years of age and older. (See Dr. Ganley's memo, dated 23-Mar-2012.)

12. Labeling

The labeling negotiated during the review of Teva's 7-Feb-11 submission is acceptable to me. (The carton and container labels are found in Teva's 15-Nov-11 submission, and the consumer information leaflet is found in Teva's 7-Dec-11 submission.) This labeling is OTC labeling for all women of reproductive age.

The proposed labeling in this submission is the same as the labeling noted above, except for:

1. On the rear PDP, the following highlighted text appears
 - a. Not for sale to those under 15 years of age
 - b. Proof of age required
 - c. Not for sale where age cannot be verified
2. Within the Drug Facts Box, under "Directions," a new first bullet has been inserted that reads (b) (4)

The proposed new elements of labeling are similar to elements that appear on labeling for OTC smoking cessation aids containing nicotine except that the nicotine products have an age cut-off of 18 years of age. Of note, the safety and effectiveness of nicotine (as either a prescription or an OTC product) for smoking cessation in teens younger than 18 have not been established, and nicotine is an addictive drug.

There was no prescription labeling in the 7-Feb-11 submission, which proposed a full OTC switch, and there will be no prescription labeling in the current proposal, which proposes adding 15- and 16-year-olds to the OTC label.

I do not agree with adding the elements in bullets 1 and 2 (above) to the proposed OTC label because I continue to recommend an OTC label for consumers who need Plan B One-Step. I recognize that the proposed labeling may be no worse than current labeling for the youngest teens, and I agree with Dr. Chang that the proposal may represent an improvement for teens who are 15 and 16 by removing the delay imposed by the prescription step; however, I am

unable to recommend labeling that restricts access to a subset of women (the youngest) who may need postcoital contraception.

Dr. Chang points out in her review that “not for sale to those under 15 years of age” is at odds with [REDACTED] (b) (4). The same contradictory language appears on OTC nicotine products. Although removing the “not for sale” language would solve the contradiction, it would leave the retail clerk without a reason for checking the age of the purchaser. Dr. Chang proposed that the statement could be modified to read: [REDACTED] (b) (4). This modification is acceptable to me.

To better understand how nicotine OTC labeling is handled by pharmacists, I visited three local pharmacies. I found that local pharmacies deal with nicotine OTC labeling in different ways, but all have mechanisms in place to restrict sale to consumers who are 18 and older. I also found that, for a younger teen seeking the product for smoking cessation, labeling may compromise access, even if he or she has a prescription from a doctor in hand.

At one in-store pharmacy, nicotine OTC products were behind glass at the pharmacy counter. A consumer has to interact with a pharmacist or a clerk in the pharmacy section to access the product. The pharmacist stated she would not fill a prescription for a nicotine product for a 16-year-old without first checking for advice from her pharmacy board (because of the “not for sale to those under 18 years of age” text). She did not know how long the process of clearing the sale with her pharmacy board would take. At another pharmacy, the nicotine OTC products were near the front cash registers, to one side of the cigarettes and well away from the pharmacy section. The products could be directly accessed by a consumer, but the retail clerk stated that she must check IDs on anyone who looks younger than 40 years of age at the time of purchase. I asked a pharmacist how she would handle a prescription for a nicotine product for a 16-year-old. She said she would fill the prescription, despite the “not for sale” labeling, because a prescription addressed the [REDACTED] (b) (4) part of labeling. At another store, the nicotine OTC products were in the pharmacy section of the store, could be accessed by a consumer without an intermediary, and could be brought to a self-checkout counter. However, when I tried to purchase a product at the self-checkout, I received an electronic message to wait for an attendant. The attendant appeared promptly. The procedures in each pharmacy were different, but all accomplished the age verification. However, it was clear that the “not for sale” language may prevent access for a young teen who presents with a prescription. This would likely also be true for Plan B One-Step.

Several facts mitigate the access problem imposed on younger women by the proposed Plan B One-Step labeling. Younger women will still be able to obtain it through clinics where they interact with healthcare providers, fulfilling the [REDACTED] (b) (4) element of labeling. Additionally, the related two-dose levonorgestrel product is available to younger teens through its prescription labeling. (However, the company’s argument that the new label will provide the product to 99% of current users seems tautological as current labeling imposes a substantial barrier (a prescription requirement) on teens younger than 17.)

The proposed label for Plan B One-Step shares with the current dual labeling the burden of age verification. Age verification is a burden both for the pharmacy staff and the consumer. Requiring ID may delay access as some women may not have proof-of-age ID when they

arrive at a pharmacy seeking this time-sensitive product. Making the product OTC without age restriction would resolve the problem of needing an ID with proof of age.

Teva has asked to be relieved of the responsibilities of the CARE Program, which monitored pharmacy compliance with the dual prescription/OTC labeling, because removal of prescription labeling renders the CARE Program obsolete. Whether or not the current application is approved, I agree that the CARE Program may end. The results of the Program have been reviewed repeatedly by Dr. Davis of the FDA, and his reviews have shown that pharmacies have successfully managed the dual labeling. There is no reason to continue the CARE Program indefinitely, and, if OTC labeling is approved, the Program no longer applies.

A labeling review by the labeling review team was pending when this review was finalized.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

My recommendation is a complete response action because I continue to recommend OTC labeling for all women of reproductive age. This was the review team's previous recommendation, and there is nothing in the current submission to support a change in that recommendation.

21CFR§330.10(a)(4)(vi) states "A drug shall be permitted for OTC sale and use by the laity unless, because of its toxicity or other potential for harmful effect or because of the method or collateral measures necessary to its use, it may safely be sold and used only under the supervision of a practitioner licensed by law to administer such drugs." It remains my opinion that Plan B One-Step has fulfilled the regulatory conditions for OTC sale.

OTC labeling would allow women of reproductive age the same rapid access to Plan B One-Step that all men have to condoms. Rapid access to Plan B One-Step matters: time is of the essence for effectiveness. Women must obtain this easy-to-use product in the short window of time during which it offers any effectiveness. Preventing unplanned pregnancies with a safe product is an important public health goal. There is no medical reason for making it difficult for a subset of women (the youngest) to prevent unplanned pregnancy. Condoms are available over-the-counter. Requiring all men who need condoms to present proof of age and men who are younger than 17 (or 15) to first obtain a prescription from their doctors would not serve the public health. Imposing these requirements on women who need Plan B One-Step does not serve the public health either.

Additional consumer data are unnecessary for approval. Plan B One-Step is a low-risk product with a simple label. Furthermore, Plan B One-Step is provided only in packaging that contains a single pill per package. The labeling compares favorably to the labeling of many OTC products, for example, cough-cold products, painkillers, and acid reducers, to name only a few OTC products that have more complex dosing regimens and that may be purchased in larger quantities by consumers of any age.

Typically, I would recommend that labeling be negotiated during the review cycle. If Teva provided acceptable OTC labeling for all women of reproductive age, I would recommend approval. However, this is not a typical review cycle as the Secretary of HHS has already determined that OTC labeling for all women of reproductive age is not acceptable. Whether Teva's proposed label and marketing plan adequately address Secretary Sibelius' concerns is unclear to me. The Secretary did not specify the details of a path (or paths) forward in her memo of 7-Dec-2011.

I agree with the primary clinical reviewer that the proposed label is likely to be an improvement over (and is certainly no worse than) current labeling. At the time this review was finalized, Plan B and its generics, the two-dose levonorgestrel products for the same indication, remain dual-labeled products, and therefore women must interact with the pharmacist to obtain them. Access to any levonorgestrel postcoital contraception for women would not be impaired, and may be improved for 15- and 16-year-olds, if Plan B One-Step is marketed OTC with the proposed label.

Nonetheless, I do not agree with the current proposal. Plan B One-Step has met the regulatory requirements for OTC marketing. Teva's current proposal continues an unnecessary burden of age verification on pharmacy staffs and women who need the product; continues to delay access to a time-sensitive product for women who do not have proof of age on hand; and continues the prescription road-block for teens younger than 15. I continue to recommend OTC labeling for all women of reproductive age.

- Risk Benefit Assessment

The data in the submission do not impact my previous risk benefit assessment. (See attached review.) No unexpected safety issues were detected in the postmarketing data.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Standard postmarketing pharmacovigilance is appropriate. I agree that Teva should be relieved of responsibilities of the CARE program.

- Recommendation for other Postmarketing Requirements and Commitments

None

- Recommended Comments to Applicant

I recommend relieving Teva of the responsibilities of the CARE program.

14. Appendix

Cross-Discipline Team Leader Review

Date	25-Oct-2011
From	Lesley-Anne Furlong, MD, FACOG
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 21-998, Supplement S-002 (studies conducted under IND 74294)
Applicant	Teva Women's Health, Inc.
Date of Submission	7-Feb-2011
PDUFA Goal Date	7-Dec-2011
Proprietary Name / Established (USAN) names	Plan B One-Step/levonorgestrel
Dosage forms / Strength	Tablet/1.5 mg
Proposed Indication(s)	reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)
Recommended:	<i>Approval pending satisfactory negotiation of labeling</i>

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1. Introduction

This is a summary review of an efficacy supplement that seeks to change the marketing status of Plan B One-Step from prescription to over-the-counter for women who are younger than 17 years of age. Plan B One-Step is already approved as an over-the-counter (OTC) drug for women of reproductive age who are 17 years of age and older. To support the change in marketing, the submission contains

- A final study report for a label comprehension study
- A final study report for an actual use study
- A literature review
- An analysis of postmarketing safety
- Proposed labeling

FDA has already determined that Plan B One-Step has a favorable benefit-to-risk profile for all women of reproductive age, and the submission does not re-visit that determination.

2. Background

Plan B One-Step is a single-dose levonorgestrel product indicated to reduce the chance of pregnancy after unprotected sex. Plan B One-Step has a complicated regulatory history enmeshed with the regulatory history of Plan B, a two-dose levonorgestrel 0.75 mg tablet with the same indication. Details of the regulatory history are provided in Dr. Christina Chang's primary clinical review. A brief summary of the scientific and regulatory background follows.

The active ingredient in Plan B One-Step is levonorgestrel, a synthetic progestin with a long history of use in female contraceptives. Norgestrel, a racemic mixture of levonorgestrel and dextro-norgestrel, was first approved in 1968 in a combination birth control pill. FDA's Orange Book currently lists 20 combination birth control pills containing both levonorgestrel and an estrogen. Levonorgestrel is also found as a single ingredient in FDA-approved contraceptive implants and an intrauterine device. FDA has no open safety issues for levonorgestrel. Progestin-containing hormonal contraceptives are indicated for women of reproductive age, including teens, who need contraception. Except for Plan B and Plan B One-Step, contraceptive products containing progestins do not have age-specific labeling for subgroups of women of reproductive age. The age-specific labeling of Plan B and Plan B One-Step was a result of the unusual participation of the Agency's acting director and the acting commissioner in the approval process (see below).

FDA approved Plan B (NDA 21-045) in

- July 1999 as a prescription product
- August 2006 as an OTC product for women 18 years and older and a prescription product for women younger than 18 years
- July 2009 as an OTC product for women 17 years and older and as a prescription product for women younger than 17 years

FDA approved Plan B One-Step (NDA 21-998) in

- July 2009 as an OTC product for women 17 years and older and a prescription product for women younger than 17 years

In April 2003, the applicant submitted a supplement to NDA 21-045 to switch Plan B from prescription to OTC status. In 2004, two CDER review offices and an advisory committee composed of members of the Nonprescription Drug Advisory Committee and the Advisory Committee for Reproductive Health Drugs recommended approval of an Rx-to-OTC switch for Plan B. However, on May 6, 2004, Dr. Steven Galson, the acting director of the Center for Drug Evaluation and Research (CDER), over-rode the recommendation for approval. Dr. Galson issued a Not Approvable letter because of “the lack of available data relevant to OTC use of the product by adolescents younger than 14 and very limited data in the 14-16 age group.”

In July 2004, the applicant submitted a Complete Response to the Not Approvable letter. The Complete Response proposed to switch Plan B to OTC status for women age 16 and older and to keep Plan B as a prescription product for women under 16. On August 26, 2005, Dr. Galson wrote a memo addressing the Complete Response and discussing his concerns about Plan B use by teens. In his memo, Dr. Galson contended that additional data on actual use and label comprehension were needed in women younger than 17 years of age. Subsequently, the acting FDA commissioner, Dr. Andrew von Eschenbach, decided that 18 years was the appropriate age cut-off because of the general retail familiarity with enforcing 18 as a cutoff age for restricted sale of other commercial products.

In August 2006, Plan B was approved as an OTC product for women 18 years and older and remained Rx for women younger than 18 years of age. Plan B thus became the only FDA-approved contraceptive product with OTC labeling for a subset of women of reproductive age. In contrast, condoms have a long history of FDA-approval as OTC products for all men, including teenagers, without regard to age. Spermicides are also available OTC without age restrictions to those who need contraception.

When Plan B One-Step was approved in 2009, both Plan B and Plan B One-Step were labeled as prescription products for teens younger than 17 years of age in response to a court mandate and with the scientific concurrence of the FDA review team.

The applicant and the FDA had a series of interactions between 2007 and 2010 related to the data needed to address Dr. Galson’s concerns about OTC availability of Plan B and Plan B One-Step for younger teens. In meetings and advice letters, FDA provided general advice as well as specific comments about the protocols for a label comprehension study (LCS) and an actual use study (AUS) for Plan B One-Step. During the meeting held in June 2009, FDA told the applicant that, to support a full OTC switch of Plan B, Dr. Galson’s concerns articulated in his memos of August 26, 2005 and May 6, 2004 would need to be addressed; the same advice would apply to a proposal to market Plan B One-Step as an OTC product for women of all ages.

Comment: The submission under review was the result of a series of interactions between the applicant and the FDA. I have personally reviewed the written record of the interactions and conclude that the applicant has adequately followed FDA advice related to the LCS, AUS, and overall content of the submission.

The present submission focuses on supporting OTC access to Plan B One-Step for teens who are younger than 17 years old. The submission addresses Dr. Galson's concerns about whether younger teens can use of Plan B One-Step without the intervention of a healthcare provider; that is, whether younger teens can adequately follow the OTC labeling.

To prepare this summary review, I have reviewed the applicant's submission and the following FDA reviews:

- clinical review by Christina Chang, Medical Officer
- social science review by Murewa Oguntimein, Social Scientist
- statistical review by Rima Izem, Biostatistician
- clinical inspection summary by Sharon Gershon of FDA's Office of Scientific Investigations
- labeling reviews by Maria Ysern, Interdisciplinary Scientist
- consult review by Lisa Mathis, Director of Pediatric and Maternal Health Staff
- 915 review of first 18 months of postmarketing data for Plan B One-Step by FDA's Office of Surveillance and Epidemiology and the Division of Reproductive and Urologic Drugs

3. CMC/Device

Not applicable

4. Nonclinical Pharmacology/Toxicology

Not applicable

5. Clinical Pharmacology/Biopharmaceutics

Not applicable

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

As noted above, efficacy has already been demonstrated for Plan B One-Step. Baseline and follow-up pregnancy tests were not performed during the actual use study unless clinically indicated.

Seven pregnancies were reported during the follow-up period of the actual use study and are discussed in Section 8.2. None of the pregnancies were the result of incorrect use of Plan B One-Step; that is, none of the pregnancies resulted from misinterpretation of OTC labeling.

8. Safety

8.1 Label Comprehension Study (DR-LEV-301)

The social scientist, Oluwamurewa Oguntimein, reviewed the design and findings of the label comprehension study (LCS) in detail. The statistical reviewer, Dr. Rima Izem, confirmed the applicant's primary analyses. A summary of the LCS is presented here.

The purpose of the study was to estimate the proportion of young women aged 12-17 years who understood each of the following key elements of labeling:

1. Plan B One-Step is indicated for prevention of pregnancy after unprotected sex
2. Plan B One-Step should be taken as soon as possible after sex
3. Plan B One-Step does not prevent sexually transmitted diseases or HIV/AIDS
4. Plan B One-Step should not be used in place of regular contraception
5. Plan B One-Step should be taken within 72 hours after sex
6. Plan B One-Step should not be used by women who are already pregnant

From two to four questions were used to test each element. A total of 377 subjects were recruited at eight shopping malls and clinics sites; 335 met all inclusion criteria and became the primary analysis population (the "Eligible Population"). Most (n=290) subjects were recruited at malls; the remaining 45 subjects were recruited at clinics. Various minimum quotas (in addition to age) were pre-specified to ensure diversity:

- African American, 25%
- Hispanic, 20%
- 7th grade literacy or lower, 20%
- no prior emergency contraceptive use, 75%

The planned analysis was the proportion of subjects who understood each concept for the overall population and for a variety of predefined subgroups. The sample size for each age range, other subgroup quotas, and the elements of labeling to test were negotiated with the FDA before the study started.

During the study, the applicant discovered research misconduct at two sites (Chicago and Miami) during an investigation of handwriting irregularities from these sites. The misconduct

involved unauthorized and untrained personnel completing data forms at these two sites; the forms were then signed by the trained site staff. As a result, enrollment was terminated at these two sites and the data from the sites (n=67) were not used in the analysis.

The pre-specified demographic quotas were met and exceeded. The eligible population included between 54 and 59 subjects of each age between 12 and 17 years of age (see Table 1). Among the eligible population, 21% were Hispanic, 26% were African Americans, 42% were low literacy (defined as a REALM-Teen score of 58 or lower), and 7% reported previous use of emergency contraceptive pills.

Table 1. Eligible Population by Age Group

Age	N
12	54
13	56
14	54
15	59
16	57
17	55
Total	335

Source: derived by reviewer from applicant's final study report, Table 2.1a

Table 2 summarizes the understanding of the key concepts by the entire study population. At least 82.7% of subjects understood each of the six concepts. The least well understood concept was that Plan B One-Step should be taken as soon as possible after sex (82.7%).

Table 2. Study Subjects Understanding of Key Concepts

Key Concepts	Subjects who understand n (%) N=335
1. Plan B One-Step is indicated for prevention of pregnancy after unprotected sex	300 (89.6%)
2. Plan B One-Step should be taken as soon as possible after sex	277 (82.7%)
3. Plan B One-Step does not prevent sexually transmitted diseases or HIV/AIDS	310 (92.5%)
4. Plan B One-Step should not be used in place of regular contraception	309 (92.2%)
5. Plan B One-Step should be taken within 72 hours after sex	319 (95.2%)
6. Plan B One-Step should not be used by women who are already pregnant	320 (95.5%)

Source: derived by reviewer from applicant's final study report, section 10.2.3

The applicant performed a variety of exploratory subgroup analyses by demographic characteristic and by question. The subgroup analyses related to enrollment quotas are summarized in the tables that follow.

Table 3 summarizes the understanding of key concepts by age. Overall, the understanding of key concepts was similar from 12 to 17 years of age. Key concept #2, related to timing of pill ingestion, trends to being less well understood by the youngest subjects; however, these subjects appeared to understand key concept #5, also related to timing of pill intake, as well as the older subjects.

Table 3. Understanding of Key Concepts by Age, Primary Eligible Population

	Age					
	12 N= 54 %	13 N= 56 %	14 N= 54 %	15 N= 59 %	16 N=57 %	17 N=55 %
1. Plan B One-Step is indicated for prevention of pregnancy after unprotected sex	87	82	85	95	91	96
2. Plan B One-Step should be taken as soon as possible after sex.	78	77	83	88	83	87
3. Plan B One-Step does not prevent STDs or HIV/AIDS	91	88	87	98	95	96
4. Plan B One-Step should not be used in place of regular contraception	93	88	91	93	93	96
5. Plan B One-Step should be taken within 72 hours after sex.	98	89	89	98	98	98
6. Plan B One-Step should not be used by women who are already pregnant	94	95	91	98	97	98

Source: derived by reviewer from applicant's table 5.1.d, p. 124, final study report for LCS

Regarding race (Table 4), Whites trended toward understanding the key concepts somewhat better than African Americans and Others. Hispanic ethnicity did not seem to impact label comprehension, except possibly for a trend toward greater understanding of key concept #2 among Hispanics (Table 5). Lower literate subjects trended toward less understanding of all six key concepts (Table 6), and prior users of ECs tended to have somewhat better comprehension of key concepts than subjects who had never used ECs (Table 7).

Table 4. Understanding of Key Concepts by Race, Primary Eligible Population

	White only	Race African American	Other
	N= 163	N= 88	N=74
	%	%	%
1. Plan B One-Step is indicated for prevention of pregnancy after unprotected sex	95	88	89
2. Plan B One-Step should be taken as soon as possible after sex.	90	73	87
3. Plan B One-Step does not prevent sexually transmitted diseases or HIV/AIDS.	97	91	92
4. Plan B One-Step should not be used in place of regular contraception	97	90	92
5. Plan B One-Step should be taken within 72 hours after sex.	98	94	100
6. Plan B One-Step should not be used by women who are already pregnant	98	98	96

Source: derived by reviewer from applicant's Table 5.1c, p. 125 of final study report for LCS

Table 5. Understanding of Key Concepts by Ethnicity, Primary Eligible Population

	Hispanic	Non-Hispanic
	N= 70	N= 254
	%	%
1. Plan B One-Step is indicated for prevention of pregnancy after unprotected sex	93	92
2. Plan B One-Step should be taken as soon as possible after sex.	93	83
3. Plan B One-Step does not prevent STDs or HIV/AIDS	94	95
4. Plan B One-Step should not be used in place of regular contraception	93	94
5. Plan B One-Step should be taken within 72 hours after sex.	100	97
6. Plan B One-Step should not be used by women who are already pregnant	97	98

Source: derived by reviewer from Table 5.1f, p 126 final study report for LCS

Table 6. Understanding of Key Concepts by Literacy Level, Primary Eligible Population

	Literacy Level	
	7th grade or lower N= 140 %	8 th grade or higher N= 195 %
1. Plan B One-Step is indicated for prevention of pregnancy after unprotected sex	82	95
2. Plan B One-Step should be taken as soon as possible after sex.	74	89
3. Plan B One-Step does not prevent STDs or HIV/AIDS	84	99
4. Plan B One-Step should not be used in place of regular contraception	87	96
5. Plan B One-Step should be taken within 72 hours after sex.	92	97
6. Plan B One-Step should not be used by women who are already pregnant	92	98

Source: derived by reviewer from applicant's Table 5.1.g, p. 127 of final study report for LCS

Table 7. Understanding of Key Concepts by Ever Use of Emergency Contraceptive Pills, Primary Eligible Population

	Prior use	Never used
	N= 24 %	N= 311 %
1. Plan B One-Step is indicated for prevention of pregnancy after unprotected sex	100	89
2. Plan B One-Step should be taken as soon as possible after sex.	83	83
3. Plan B One-Step does not prevent sexually transmitted diseases or HIV/AIDS	100	92
4. Plan B One-Step should not be used in place of regular contraception	96	92
5. Plan B One-Step should be taken within 72 hours after sex.	100	95
6. Plan B One-Step should not be used by women who are already pregnant	100	95

Source: derived by reviewer from applicant's Table 5.1h, p. 128 of final study report for LCS

The applicant also provided a historical comparison between this LCS and the LCS done in 2001 for Plan B (see Appendix 8 of the final study report). The 2001 study included 656 subjects from 12 to 50 years old, most of whom (n=580) were 17 years and older. The 2001 study was of similar design and 13 questions in both studies overlapped. The proportions of subjects who answered correctly were similar for 11 of 13 questions. In the two questions with the greatest difference between groups, the older study had a greater percentage of incorrect responses. Both of these questions were related to the instruction to take the tablets as soon as possible after sex.

Comments: The social science reviewer commented that the study demonstrated that adolescents were able to understand the key elements of labeling; I concur.

The applicant followed the advice of the FDA regarding the design and conduct of the LCS. Overall, the understanding of labeling was acceptable. The younger teens trended toward having a lower understanding of one element related to dose timing (“as soon as possible”) but had a similar understanding of a second element related to dose timing (“within 72 hours”) compared with older teens. Whether the findings of the subgroup analyses represent chance variation related to exploratory analyses is unknown; however, I do not expect the findings to be of clinical significance. As subjects understood that the product should be taken within 72 hours after sex, efficacy should be acceptable.

It is important to note that one of the questions testing the second element (“as soon as possible”) was ambiguous and may have contributed to the lower overall understanding of the element compared with the other five elements (see social science review.) With the caveat that cross-study comparisons have pitfalls, historical data from a similar study for Plan B found a greater percentage of generally older subjects had a lower understanding of element 2 (“as soon as possible”) than the younger subjects in the Plan B One-Step study.

That OTC access may shorten the time interval between a contraceptive failure and use of Plan B One-Step is self-evident; obtaining an OTC drug requires only a trip to the pharmacy, whereas obtaining a prescription typically requires contacting a healthcare provider, an appointment to obtain a prescription, and a trip to the pharmacy. It can be difficult for this to all occur within 72 hours. OTC access may therefore improve efficacy for young teenagers who currently must have a prescription to purchase Plan B One-Step.

The comprehension of key elements in this LCS is akin to the numbers seen in LCS studies that have supported approval of other OTC products. It is typical for low literacy numbers to be less robust than those of the general population. The numbers for subjects of low literacy are not atypical and are acceptable.

An LCS identifies elements of labeling that are not adequately understood, and this Plan B One-Step LCS showed that the tested elements of labeling were adequately understood by the various subgroups assessed. However, an LCS does not test consumer behavior because participants in an LCS study are not seeking to use the product. In addition, the design of a LCS may impact the way subjects interact with labeling. Actual consumer behavior can be evaluated in an actual use study (AUS). For this proposed OTC switch, the applicant performed an AUS, which is summarized in the following section.

8.2 Actual Use Study (DR-LEV-302)

The actual use study (AUS) is reviewed in detail in Dr. Chang’s primary clinical review. I have read Dr. Chang’s review and agree that the results of the AUS support that adolescents can appropriately and safely use Plan B One-Step in an OTC setting. Dr. Chang recommended approval of the application pending satisfactory negotiation of labeling. Dr. Izem performed a statistical review of the AUS and was able to reproduce the applicant’s findings for the primary endpoints from the study datasets. A brief summary of the AUS follows.

AUS Study Design and Objectives:

The AUS was an open-label, single-arm, naturalistic study to determine the percentage of subjects who correctly self-select and use Plan B One-Step under simulated OTC conditions. The study sought to enroll subjects 11 to 17 years old who were seeking emergency contraception (EC).

Each subject read the label without assistance. The study product was dispensed only to those subjects who appropriately self-selected and agreed to participate. Follow-up occurred at one, four, and eight weeks. Subjects were asked about product use, health problems since last contact, and pregnancy status. Subjects were also asked about repeated use of EC since enrollment, and charts were evaluated for repeat use as well. Sample size was negotiated with FDA and ultimately the study was to include a minimum of 25 females of each age, 14 through 17 years, and any subjects from 11 to 13 years who were eligible to participate. The originally agreed-upon number of subjects in the 11- to 13-year age range was 25, but, after two years of study experience, enrollment in that age range was minimal. FDA agreed to a protocol amendment to continue to enroll 11- to 13-year olds without a minimum number of enrollees after the applicant presented their interim enrollment data and provided literature showing that difficulty enrolling younger subjects was to be expected. When Plan B One-Step was approved in July 2009 as an OTC product for women 17 years of age and older, the AUS protocol was amended to no longer recruit 17-year-olds.

The co-primary objectives of the study were to determine the percentage of subjects who appropriately self-selected and the proportion of subjects who correctly used Plan B One-Step under simulated OTC conditions. Correct self-selection was defined as wanting to use the product for its indication AND not having an allergy to levonorgestrel, a positive pregnancy test, or a known pregnancy. Correct use was defined as taking Plan B One-Step within 72 hours following unprotected sex.

The secondary objectives were to estimate the incidence of adverse events and repeat use of emergency contraception during the 8-week follow-up period. Adverse events were captured at regularly scheduled telephone contacts or return visits by asking if the subject had had any health issue since the last contact.

AUS Study Results:

A total of 343 subjects were enrolled in the AUS. Table 8 shows the age range of enrolled subjects. Clinics were unable to enroll any subjects younger than 13 years of age because no subjects in this age range presented for emergency contraception. The race distribution was 42.9% Latina, 19.8% Asian/Pacific Islanders, 14.0% African-American, and 11.4% White.

Approximately 40% of subjects had used EC previously, with the percentage increasing with age (ranging from 0% of 13-year-olds, to 66.2% of 17-year-olds). Approximately 29.4% of subjects reported no previous use of contraception with the percentage decreasing by age (66.7% of 13-year-olds, to 15.4% of 17-year-olds). Approximately 88.3% had never been

pregnant, with the percentage decreasing with increasing age (100% of 13 year olds to 81.5% of 17 year olds).

Table 8. Number of Subjects and Prior Use of Contraception by Age in AUS

Age of Subjects	13 years old	14 years old	15 years old	16 years old	17 years old
N	3	35	100	140	65
No previous use of contraception	66.7%	51.4%	31%	28.6%	15.4%

Source: Applicant's Submission, Clinical Study Report, Table 8

By the applicant's analysis, results of the primary objectives for the enrolled population were:

- 90.1% appropriately self-selected
- 88.6% of those who appropriately self-selected correctly used the product within 72 hours of intercourse

Comment: Most teens were able to correctly self-select, and among those who correctly self-selected, most also correctly used the product.

The primary clinical review by Dr. Chang contains a detailed analysis of reasons for inappropriate selection and use, and the expected consequences. Dr. Chang noted that the applicant's definitions were conservative, particularly when the clinical consequences are considered. For example, the most common reason that resulted in being coded as an inappropriate self-selector was "might be pregnant." (25 of 34 adolescents); however, subsequent responses suggested that many thought they "might be pregnant" only because they had had unprotected sex. In Dr. Chang's review, she considered only two subjects as inappropriate self-selectors because they had positive pregnancy tests at the time of self-selection. It is worth noting that although these two subjects would derive no benefit from the use of Plan B One-Step, the risks (for example, nausea) are minor.

Similarly, Dr. Chang's analysis of the reasons for being coded as an incorrect user showed that the applicant's definition of incorrect use was conservative. By exploring the datasets, Dr. Chang found that the applicant coded eleven subjects as incorrect users because the subjects did not follow-up within 10 days of the clinic visit; however, these eleven subjects used Plan B One-Step correctly (that is, within 72 hours of the index episode of unprotected sex.) Excluding these subjects from the "incorrect user" population produces gives a correct use percentage of 92.3%. This is very close to the findings of the AUS study conducted to support the OTC switch of Plan B, where 92.4% of subjects took the first dose of Plan B within 72 hours of unprotected intercourse. I have considered Dr. Chang's analysis and agree that the study has demonstrated acceptable use of Plan B One-Step by teens.

Table 9 and Table 10 show exploratory analyses of the primary endpoint by age. Overall, there are no clear trends by age.

Table 9. Proportion of Enrolled Population that Appropriately Self-Selected by Age (Years)

	13	14	15	16	17
Number of Subjects	3	35	100	140	65
Appropriate Self-Selection	2 (66.7%)	30 (85.7%)	91 (91.0%)	128 (91.4%)	58 (89.2%)

Source: Applicant's Submission, Clinical Study Report, Table 18

Table 10. Proportion of Treated Population Demonstrating Correct Product Use within 72 Hours after Intercourse by Age (Years)

	13	14	15	16	17
Number of Subjects	1	30	87	123	56
Product Use within 72 Hours	1(100%)	24 (80.0%)	78 (89.7%)	107 (87.0%)	53 (94.6%)

Source: Applicant's Submission, Clinical Study Report, Table 19

Comments: Results support that the large majority of teens can use OTC labeling to appropriately self-select and use Plan B One-Step. There was no clear trend in proportion of correct self-selection or correct use by age, although more older teens than younger teens sought to use Plan B One-Step. (The drop-off in number of enrollees at age 17 was the result of a protocol amendment that stopped recruitment of 17-year-olds after Plan B One-Step was approved as an OTC product for women 17 years of age and older.) The trend of greater use of contraception with age is consistent with my own experience as an obstetrician/gynecologist in clinical practice.

A secondary objective was measuring the repeat use of emergency contraception during the 8-week follow-up period. Most subjects reported a single use of Plan B One-Step during the study. Table 11 summarizes a subgroup analysis by age. There was no discernable trend for repeat use by age. Repeat use included one additional time (13.0%), two additional times (5.4%), or three additional times (0.7%).

Table 11. Repeat Product Use in the Completed Follow-Up Population (N=277) by Age (Years) at Screening

Number of repeat uses	13	14	15	16	17
None	1 (100%)	22 (84.6%)	64 (78.1%)	92 (81.4%)	45 (81.8%)
1	0	1	12	19	6
2	0	3	6	3	4
3	0	0	1	1	0

Source: Applicant's Submission, Clinical Study Report, Table 28

Comment: Most teens did not repeat use during the 8-week follow-up period and there was no trend for repeat use by age. None of the teens used Plan B One-Step more than 3 times in 8 weeks.

The analysis of repeat use adequately addressed Dr. Galson's concern that teens might substitute the product for routine and more effective contraception. I do not, however, agree with Dr. Galson's concern. It is not within FDA's purview to require that a person use the most effective birth control method available (or, for that matter, the most effective

antihypertensive or heartburn drug available). Condoms are not the most effective contraceptives, but FDA does not restrict access to condoms because condoms may be substituted for more effective methods. It is also not within the FDA’s purview to require that routine contraception be used by sexually active people. The decision to use birth control and the choice of birth control method depend on many factors (sexual frequency, level of concern about pregnancy, price, access, concern about sexually-transmissible infection, contraindication to a particular method, to name just a few.) For the youngest teens in the study, most had used no contraception in the past. Use of Plan B One-Step once or intermittently can be a reasonable choice.

The other secondary objective was to estimate the incidence of adverse events. There were no deaths and one serious adverse event was reported (a miscarriage). Miscarriage is a common outcome of pregnancy and there is no evidence that progestins are causally related to miscarriage. Other adverse events were reported infrequently and no unexpected adverse events occurred. Without a control group to provide a background frequency for the reported adverse event, the contribution of drug to the adverse events reported is unclear; however, there were no worrisome or unexpected findings. The most frequently reported adverse events were nausea, headache, and menstrual irregularity.

Table 12. Frequency of Reported Adverse Events in $\geq 1\%$ of the Safety Population: Subjects Who Reported Any Use of Plan B One-Step

Adverse Event (MedDRA Preferred Term)	Total Number of Subjects = 299 N (%)
Nausea	8 (2.7%)
Headache	8 (2.7%)
Menstruation Irregular	6 (2.0%)
Vaginal Bleeding*	4 (1.3%)
Pelvic Pain	4 (1.3%)
Influenza	3 (1.0%)
Vulvovaginal Mycotic Infection	3 (1.0%)
Vaginal Spotting*	3 (1.0%)
Dizziness	3 (1.0%)
Abdominal Pain Upper	3 (1.0%)
Fatigue	3 (1.0%)
Vomiting	3 (1.0%)

*Vaginal Bleeding, regardless of severity, codes in MedDRA to a Preferred Term of “Vaginal Haemorrhage.” Therefore, for clarity, the applicant used the MedDRA Lower Level Term rather than the Preferred Term
 Source: Applicant’s Submission, Clinical Study Report, Table 29

Subjects reported seven pregnancies, only one of which was reported by investigators as an adverse event. The pregnancy data are summarized in Table 13.

Table 13. Summary of Pregnancies

Site/Subject	Age (Years)	Used Plan B within 72 hours of unprotected intercourse	Comments	Outcome
1/0107	16	Yes (one day after unprotected sex)	By 8-week ultrasound, conceived on or shortly after the index episode of unprotected sex	Surgical termination
1/0131	14	Yes (one day after episode of unprotected sex for which she presented to the clinic)	By 13-week ultrasound, was about 1 week pregnant when she took Plan B-One Step (too early for self-diagnosis or positive pregnancy test)	Surgical termination
1/0302	17	Yes (two days after unprotected sex)	By 7-week ultrasound, conceived shortly after the index episode of unprotected sex.	Surgical termination
1/0362	16	Yes (two days after unprotected sex)	By 7-week ultrasound, conceived on or shortly after the index episode of unprotected sex.	Surgical termination
1/0384	16	Yes (one day after unprotected sex)	By 26-week ultrasound, conceived after the index episode of unprotected sex	Delivered healthy infant at 36.5 weeks gestation
1/0405	16	Yes (one day after unprotected sex)	By 7-week ultrasound, conceived on or shortly after the index episode of unprotected sex	Ongoing pregnancy
1/0502	16	Yes (one day after unprotected sex)	Negative pregnancy test two weeks after taking Plan B One-Step; positive 3 weeks after taking Plan B One-Step; therefore, likely conceived after the index episode of unprotected sex.	Miscarriage

Source: Derived by reviewer from pregnancy narratives and review of case report forms in Applicant's submission, Clinical Study Report

Comments: The pregnancy data do not support a relationship of age to lack of efficacy. The pregnancy data also do not support a lack of efficacy related to inappropriate use. By ultrasound dating, one young woman may have been pregnant when she took Plan B One-Step, but she was too early in gestation (1 week post conception) to have missed a period and suspected pregnancy. Her use of Plan B One-Step was therefore appropriate. All women who became pregnant used Plan B One-Step as directed on the OTC labeling. Some pregnancies are expected to occur despite correct use: Plan B One-Step reduces, but does not eliminate, the chance of pregnancy after unprotected sex. In clinical trials, approximately 84% of expected pregnancies were prevented.

At the time the clinical study report was finalized, 12 subjects had not completed all three follow-up contacts; however, their drug usage information was available when the clinical study report was finalized. The applicant provided their follow-up information in the 120-day

safety update submitted during the review cycle. No adverse events and no additional drug usage were reported for the 12 subjects.

8.3 Postmarketing Spontaneous Reports

Of 69 countries in which levonorgestrel 1.5 mg is legally marketed, 32 market the product as an OTC drug. There have been no regulatory or marketing authorization actions taken for safety reasons, and the product has not been withdrawn from or restricted in any market for safety reasons. Between Jul-09 and Jan-11, approximately [REDACTED]^{(b) (4)} tablets of Plan B One-Step were distributed in the United States.

The applicant provided summaries of postmarketing reports from three databases:

- Teva's internal database (10-Jul-2009 through 30-Nov-2010)
- The World Health Organization (WHO) database (10-Jul-2009 through 15-Feb-2011)
- The FDA's AERS database (10-Jul-2009 through 30-Sep-2010)

Contents of these three databases are expected to overlap considerably because of regulatory reporting requirements; the databases contain foreign reports as well as U.S. reports.

The applicant also provided a 120-day safety update during the review cycle; the safety update referred to the periodic adverse drug experience report (PADER) for the reporting period of 1-Jan-2011 to 31-Mar-2011. The applicant was not conducting any clinical trials at the time the update was submitted.

Abuse potential is an important consideration when deciding whether a drug should be OTC. There is no evidence in its long marketing history that levonorgestrel is a drug with abuse or even overuse potential. Levonorgestrel is not known to have any stimulant pharmacologic properties. According to the current package insert, "there are no data on overdosage with Plan B One-Step, although the common adverse event of nausea and associated vomiting may be anticipated." The fact that the product packaging contains only one pill presents a practical barrier to impulsive overdosing. The fact that an overdose leads to unpleasant effects (nausea and vomiting) makes it highly unlikely that levonorgestrel will ever be a popular drug of abuse. The applicant's preliminary review of the databases from the Drug Abuse Warning Network (DAWN) and the American Association of Poison Control Centers (AAPCC) indicated that there was no meaningful information present. The analysis of the DAWN database for 2004-2009 indicated there were no DAWN reports for contraceptives during that time. Under the category "progestins," a rate of 0.1 cases per 100,000 population was reported for 2008, and no cases were reported for 2004-2007 or 2009. The analysis of the AAPCC database for 2008 and 2009 did not detect a signal for poisoning potential.

Comment: Based on a long history of safe use, lack of stimulant effect, the single-dose packaging, and the fact that vomiting occurs with higher doses, the likelihood of abuse or overuse of levonorgestrel is remote (and has not been demonstrated.)

Analysis of the postmarketing databases did not detect any new or unexpected safety signals; there was also no evidence of unique safety issues in younger teens. A brief summary of the postmarketing data by database follows.

Applicant's Internal Database

The applicant reviewed the internal postmarketing safety database for Plan B One-Step from the time of approval on July 10, 2009 through Nov 30, 2010. The search included the age range of 9 to 16 years. The youngest reporter was 13 years old. There were 332 events reported by 186 users, representing 2.4% of all events reported for the time period. The pattern of events did not show any additional risk in the younger population. One subject reported a serious, unlabelled event: vomiting blood (hematemesis). The most frequently reported adverse events for the 9-year to 16-year age range were:

- Menstruation irregular (n=106)
- Pelvic pain (n=25)
- Vomiting (n=24)
- Nausea (n=22)
- Menstruation delayed (n=19)
- Abdominal pain (n=18)
- Headache (n=18)

For comparison, the applicant tabulated all adverse events, regardless of age, over the same time period. The most frequently reported adverse events were:

- Menstruation irregular (n=4959)
- Pelvic pain (n=955)
- Vomiting (n=628)
- Nausea (n=940)
- Menstruation delayed (n=546)
- Abdominal pain (n=513)
- Headache (n=440)

Comment: The most commonly reported adverse events were the same for younger teens compared with all women. Menstrual irregularity was the most commonly reported adverse event, regardless of age.

In the FDA 915 safety review of both Plan B and Plan B One-Step, 18 cases of hematemesis, 4 of which occurred in users of Plan B One-Step, were detected in the FDA's AERS database between Jul 2007 through Dec 2010. (See Additional FDA Analysis of Postmarketing Data, below.) None of the cases were reported by healthcare providers, and details were scant. Most cases (12) were described as mild; 3 were described as severe (1 in a woman with leukemia); 3 were not rated. No age-clustering was noted. As hematemesis can occur as a complication of vomiting, a known adverse effect, it is not surprising that occasional reports of hematemesis occur. The 915 reviewers (from the Office of Surveillance and Epidemiology and the Division of Reproductive and Urologic Products) did not view the cases as a significant signal; I concur.

WHO Database

The applicant requested a search of the WHO VigiBase for reports for levonorgestrel 1.5. mg from 10-Jul-2009 through 15-Feb-2011. A total of 369 cases reporting 969 events were obtained. Among these 369 cases, 5 were in women aged 16 and under. Two of these were also in the AERS database. The remaining three reports were of breast disorder, ectopic pregnancy, and fetal abnormality (not otherwise specified).

Comment: Information from the WHO VigiBase was limited but did not detect any age-specific adverse events.

AERS Database

The applicant conducted a search of the AERS database from July 10, 2009 to 30-Sep-2010 for Plan B, Plan B One-Step, and other levonorgestrel-containing emergency contraceptive products (ECs).

For women of all ages, there were 71 cases reporting 303 adverse events for Plan B and Plan B One-Step, and an additional 28 cases reporting 66 adverse events for other levonorgestrel ECs. A total of four cases were identified in young women aged 16 and under; all reporters were 15 or 16 years of age. The four cases reported hypersensitivity-type reaction, menstrual changes, emotional distress, lack of efficacy, nausea, vomiting, and hematemesis. These events have also been reported in the older population.

Comment: Analysis of the AERS database did not reveal any age-specific safety issues.

120-Day Safety Update

The applicant was not conducting any clinical trials during the update period. There were no reports from research sites regarding any subject experiencing a serious adverse event in the AUS. A quarterly periodic adverse drug experience report (PADER) covering 1-Jan-2011 through 31-Mar-2011 did not detect any signal suggesting a change in the safety profile of Plan B One-Step or any age-specific safety issues.

Additional FDA Analysis of Postmarketing Data

During the course of the review, FDA performed a 915 review of Plan B One-Step. A 915 review occurs routinely 18 months after approval and exposure of at least 10,000 patients, whichever is later. The review entails a detailed look at postmarketing data by FDA's Office of Surveillance and Epidemiology and the Office of New Drugs, Division of Reproductive and Urologic Products. The 915 review evaluated reports received for Plan B One-Step from the time of approval through 31-Jan-2011. The reviewers concluded that "No potential safety issues were identified in this review that would warrant any labeling changes or changes in the product's safety profile."

I searched FDA's document tracking system ("DARRTS") on 7/5/2011 for open safety issues for levonorgestrel or Plan B One-Step and found none.

Comments: The analysis of postmarketing data did not detect any new safety issues. Teens experienced a similar profile of adverse events compared with all women.

8.4 Literature

The applicant reviewed the published literature for EC use and provided references. The primary clinical reviewer, Dr. Christina Chang, analyzed the references provided by the applicant and performed an independent literature review. Review of the literature did not detect any new safety issues or safety issues specific to younger women. For details, see Dr. Chang's primary clinical review.

7. Advisory Committee Meeting

An Advisory Committee meeting was unnecessary for the present submission because an Advisory Committee has already deliberated on the topic of OTC availability for Plan B in 2003. That joint Advisory Committee (Reproductive Health Drugs and Nonprescription Drugs) met to discuss the proposed switch of Plan B from Rx-to-OTC status. The joint Advisory Committee recommended by a vote of 23 to 4 that Plan B be switched to OTC availability without age restriction. As Plan B and Plan B One-Step are nearly identical (except that the Plan B One-Step dosing regimen is simpler), the review team decided there was no need to convene another Advisory Committee meeting on the same topic.

8. Pediatrics

The application did not trigger the Pediatric Research Equity Act because it did not propose a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

Dr. Lisa Mathis, Director of CDER's Pediatric and Maternal Health Staff, provided a consult review for this sNDA. Dr. Mathis concluded that the applicant has fully responded to the data needs as outlined in Dr. Galson's memos and that the studies demonstrated that women of child bearing potential of all ages can appropriately self-diagnose and administer Plan B One-Step in an OTC setting. Dr. Mathis recommended approval of the application.

9. Other Relevant Regulatory Issues

The review team requested a routine audit of the AUS study. Because the University of California, San Francisco site enrolled the majority of subjects (316 of 343 subjects), the review team selected the site for audit. The AUS study passed FDA audit: FDA's Office of

Scientific Investigations (OSI) concluded that the study was “conducted adequately and the data in support of the NDA appear reliable. OSI issued a “no action indicated” recommendation.

The applicant certified to not using the services of any person debarred under section 306 of the F, D, and C Act in connection with the application. The applicant also provided a signed certification of financial interests (Form 3454) stating that there were no financial conflicts of interest for the investigators and subinvestigators involved in the clinical study DR-LEV-302. The patent form (Form 3542a) stated that there are no relevant patents that claim the drug substance, drug product, or method of use.

10. Labeling

Only highlights of labeling appear in this review. For details of labeling, please see the reviews by Maria Ysern from the Division of Nonprescription Regulation Development.

The applicant proposed a number of changes to the already approved OTC labeling:

- Removal of the words “Rx only for women younger than age 17” from the principal display panel (PDP), and removal of the labeling by age from the Directions section of Drug Facts. These changes were acceptable to the review team and supported by the data in the submission.
- Addition of claim (b) (4) on the PDP. (b) (4)
The statement was not supported and was therefore unacceptable to the review team.
- Removal of redundant text from the consumer information leaflet; deletion of redundant text was generally acceptable to the review team.
- Replacement of “One tablet. One dose.” with (b) (4) on the PDP. The team recommended retaining the current language because the new language was not tested and there were various possible interpretations.
- Addition of the statement (b) (4) This addition was not acceptable to the review team. (b) (4)

The proprietary name was unchanged.

With removal of labeling by age, the labeling no longer has gender-specific text. While it is unlikely that men would use the product, it is reasonable to note on the label that the product is for women. I recommend adding “For women only” to the Directions section to replace the current text in Directions that says “women 17 years of age or older.”

Labeling comments were sent to the applicant. On October 21, 2011, the applicant responded with labeling revisions that addressed all but one of FDA’s concerns: removal of the claim (b) (4)

The review team did

not agree with the claim.

(b) (4)

When this review was finalized, a second labeling review to support the next round of labeling negotiations was underway.

11. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend approval of the application pending satisfactory negotiation of labeling.

- Risk Benefit Assessment

FDA approved Plan B One-Step for all women of reproductive age based on its safety and efficacy. The applicant does not seek changes in the product, its indication, the dosing regimen, or the population for whom it is indicated. The submission is limited to a proposal to change the marketing status from prescription to over-the-counter (Rx-to-OTC) for women younger than 17 years; therefore, the risk-benefit assessment focuses on the ability of younger teens to use Plan B One-Step with OTC labeling. Plan B One-Step is already marketed OTC for women who are 17 years and older.

The data from the actual use study (AUS) and label comprehension study (LCS) support that teenagers can safely and effectively use Plan B One-Step in an OTC setting. The LCS and the AUS satisfactorily addressed Dr. Galson's call for more consumer data in younger teens. The LCS study enrolled 335 young women between the ages of 12 and 17; the AUS study enrolled 343 young women between the ages of 13 and 17. Neither study detected any clinically important variation in use of the OTC labeling for Plan B One-Step with age. None of seven pregnancies reported in the AUS were the result of incorrect use of Plan B One-Step. There were no reports of unexpected adverse events in the AUS.

The applicant provided reviews of postmarketing reports and the scientific literature, and the primary clinical reviewer performed an independent review of the scientific literature. The reviews did not reveal any age-specific issues or new safety signals.

Condoms and spermicides provide a long-time precedent for OTC access to contraception regardless of age. Condoms are available OTC for anyone to purchase, and condoms may certainly be purchased by teenagers. Spermicides are similarly available OTC without age restrictions. Approval of this supplement will make labeling for Plan B One-Step consistent with labeling of other OTC contraceptives by removing the age restriction and providing the same label to all for whom the product is indicated.

The "OTC-ness" of Plan B One-Step is clear: the condition, unprotected sex, can be readily self-diagnosed and safely self-treated. Self-diagnosis requires that a woman realize that she has had unprotected sex. Self-treatment requires taking a single tablet within 72 hours of this realization. The only "do not use" conditions are allergy or pregnancy, and OTC products

have been successfully labeled with allergy and pregnancy warnings for decades. For Plan B One-Step, the pregnancy contraindication exists because the product is ineffective if a woman is already pregnant; however, there are no known risks to the pregnancy if a woman who is pregnant takes levonorgestrel. The active ingredient in Plan B One-Step is not a drug of abuse. OTC labeling for Plan B One-Step is simple compared with, for example, labeling of OTC products such as analgesics or heartburn therapies, all of which may be purchased and used by teens.

The submission adequately addressed Dr. Galson's concerns by providing data in younger women to support their ability to use Plan B One-Step with the aid of an OTC "Drug Facts" label.

I recommend that OTC access to Plan B One-Step be extended to all women of reproductive age.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None; standard postmarketing pharmacovigilance is appropriate

- Recommendation for other Postmarketing Requirements and Commitments

None

- Recommended Comments to Applicant

None

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/s/

LESLEYANNE FURLONG
05/20/2012

Cross-Discipline Team Leader Review

Date	25-Oct-2011
From	Lesley-Anne Furlong, MD, FACOG
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 21-998, Supplement S-002 (studies conducted under IND 74294)
Applicant	Teva Women's Health, Inc.
Date of Submission	7-Feb-2011
PDUFA Goal Date	7-Dec-2011
Proprietary Name / Established (USAN) names	Plan B One-Step/levonorgestrel
Dosage forms / Strength	Tablet/1.5 mg
Proposed Indication(s)	reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)
Recommended:	<i>Approval pending satisfactory negotiation of labeling</i>

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1. Introduction

This is a summary review of an efficacy supplement that seeks to change the marketing status of Plan B One-Step from prescription to over-the-counter for women who are younger than 17 years of age. Plan B One-Step is already approved as an over-the-counter (OTC) drug for women of reproductive age who are 17 years of age and older. To support the change in marketing, the submission contains

- A final study report for a label comprehension study
- A final study report for an actual use study
- A literature review
- An analysis of postmarketing safety
- Proposed labeling

FDA has already determined that Plan B One-Step has a favorable benefit-to-risk profile for all women of reproductive age, and the submission does not re-visit that determination.

2. Background

Plan B One-Step is a single-dose levonorgestrel product indicated to reduce the chance of pregnancy after unprotected sex. Plan B One-Step has a complicated regulatory history enmeshed with the regulatory history of Plan B, a two-dose levonorgestrel 0.75 mg tablet with the same indication. Details of the regulatory history are provided in Dr. Christina Chang's primary clinical review. A brief summary of the scientific and regulatory background follows.

The active ingredient in Plan B One-Step is levonorgestrel, a synthetic progestin with a long history of use in female contraceptives. Norgestrel, a racemic mixture of levonorgestrel and dextro-norgestrel, was first approved in 1968 in a combination birth control pill. FDA's Orange Book currently lists 20 combination birth control pills containing both levonorgestrel and an estrogen. Levonorgestrel is also found as a single ingredient in FDA-approved contraceptive implants and an intrauterine device. FDA has no open safety issues for levonorgestrel. Progestin-containing hormonal contraceptives are indicated for women of reproductive age, including teens, who need contraception. Except for Plan B and Plan B One-Step, contraceptive products containing progestins do not have age-specific labeling for subgroups of women of reproductive age. The age-specific labeling of Plan B and Plan B One-Step was a result of the unusual participation of the Agency's acting director and the acting commissioner in the approval process (see below).

FDA approved Plan B (NDA 21-045) in

- July 1999 as a prescription product
- August 2006 as an OTC product for women 18 years and older and a prescription product for women younger than 18 years
- July 2009 as an OTC product for women 17 years and older and as a prescription product for women younger than 17 years

FDA approved Plan B One-Step (NDA 21-998) in

- July 2009 as an OTC product for women 17 years and older and a prescription product for women younger than 17 years

In April 2003, the applicant submitted a supplement to NDA 21-045 to switch Plan B from prescription to OTC status. In 2004, two CDER review offices and an advisory committee composed of members of the Nonprescription Drug Advisory Committee and the Advisory Committee for Reproductive Health Drugs recommended approval of an Rx-to-OTC switch for Plan B. However, on May 6, 2004, Dr. Steven Galson, the acting director of the Center for Drug Evaluation and Research (CDER), over-rode the recommendation for approval. Dr. Galson issued a Not Approvable letter because of “the lack of available data relevant to OTC use of the product by adolescents younger than 14 and very limited data in the 14-16 age group.”

In July 2004, the applicant submitted a Complete Response to the Not Approvable letter. The Complete Response proposed to switch Plan B to OTC status for women age 16 and older and to keep Plan B as a prescription product for women under 16. On August 26, 2005, Dr. Galson wrote a memo addressing the Complete Response and discussing his concerns about Plan B use by teens. In his memo, Dr. Galson contended that additional data on actual use and label comprehension were needed in women younger than 17 years of age. Subsequently, the acting FDA commissioner, Dr. Andrew von Eschenbach, decided that 18 years was the appropriate age cut-off because of the general retail familiarity with enforcing 18 as a cutoff age for restricted sale of other commercial products.

In August 2006, Plan B was approved as an OTC product for women 18 years and older and remained Rx for women younger than 18 years of age. Plan B thus became the only FDA-approved contraceptive product with OTC labeling for a subset of women of reproductive age. In contrast, condoms have a long history of FDA-approval as OTC products for all men, including teenagers, without regard to age. Spermicides are also available OTC without age restrictions to those who need contraception.

When Plan B One-Step was approved in 2009, both Plan B and Plan B One-Step were labeled as prescription products for teens younger than 17 years of age in response to a court mandate and with the scientific concurrence of the FDA review team.

The applicant and the FDA had a series of interactions between 2007 and 2010 related to the data needed to address Dr. Galson’s concerns about OTC availability of Plan B and Plan B One-Step for younger teens. In meetings and advice letters, FDA provided general advice as well as specific comments about the protocols for a label comprehension study (LCS) and an actual use study (AUS) for Plan B One-Step. During the meeting held in June 2009, FDA told the applicant that, to support a full OTC switch of Plan B, Dr. Galson’s concerns articulated in his memos of August 26, 2005 and May 6, 2004 would need to be addressed; the same advice would apply to a proposal to market Plan B One-Step as an OTC product for women of all ages.

Comment: The submission under review was the result of a series of interactions between the applicant and the FDA. I have personally reviewed the written record of the interactions and conclude that the applicant has adequately followed FDA advice related to the LCS, AUS, and overall content of the submission.

The present submission focuses on supporting OTC access to Plan B One-Step for teens who are younger than 17 years old. The submission addresses Dr. Galson's concerns about whether younger teens can use of Plan B One-Step without the intervention of a healthcare provider; that is, whether younger teens can adequately follow the OTC labeling.

To prepare this summary review, I have reviewed the applicant's submission and the following FDA reviews:

- clinical review by Christina Chang, Medical Officer
- social science review by Murewa Oguntimein, Social Scientist
- statistical review by Rima Izem, Biostatistician
- clinical inspection summary by Sharon Gershon of FDA's Office of Scientific Investigations
- labeling reviews by Maria Ysern, Interdisciplinary Scientist
- consult review by Lisa Mathis, Director of Pediatric and Maternal Health Staff
- 915 review of first 18 months of postmarketing data for Plan B One-Step by FDA's Office of Surveillance and Epidemiology and the Division of Reproductive and Urologic Drugs

3. CMC/Device

Not applicable

4. Nonclinical Pharmacology/Toxicology

Not applicable

5. Clinical Pharmacology/Biopharmaceutics

Not applicable

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

As noted above, efficacy has already been demonstrated for Plan B One-Step. Baseline and follow-up pregnancy tests were not performed during the actual use study unless clinically indicated.

Seven pregnancies were reported during the follow-up period of the actual use study and are discussed in Section 8.2. None of the pregnancies were the result of incorrect use of Plan B One-Step; that is, none of the pregnancies resulted from misinterpretation of OTC labeling.

8. Safety

8.1 Label Comprehension Study (DR-LEV-301)

The social scientist, Oluwamurewa Oguntimein, reviewed the design and findings of the label comprehension study (LCS) in detail. The statistical reviewer, Dr. Rima Izem, confirmed the applicant's primary analyses. A summary of the LCS is presented here.

The purpose of the study was to estimate the proportion of young women aged 12-17 years who understood each of the following key elements of labeling:

1. Plan B One-Step is indicated for prevention of pregnancy after unprotected sex
2. Plan B One-Step should be taken as soon as possible after sex
3. Plan B One-Step does not prevent sexually transmitted diseases or HIV/AIDS
4. Plan B One-Step should not be used in place of regular contraception
5. Plan B One-Step should be taken within 72 hours after sex
6. Plan B One-Step should not be used by women who are already pregnant

From two to four questions were used to test each element. A total of 377 subjects were recruited at eight shopping malls and clinics sites; 335 met all inclusion criteria and became the primary analysis population (the "Eligible Population"). Most (n=290) subjects were recruited at malls; the remaining 45 subjects were recruited at clinics. Various minimum quotas (in addition to age) were pre-specified to ensure diversity:

- African American, 25%
- Hispanic, 20%
- 7th grade literacy or lower, 20%
- no prior emergency contraceptive use, 75%

The planned analysis was the proportion of subjects who understood each concept for the overall population and for a variety of predefined subgroups. The sample size for each age range, other subgroup quotas, and the elements of labeling to test were negotiated with the FDA before the study started.

During the study, the applicant discovered research misconduct at two sites (Chicago and Miami) during an investigation of handwriting irregularities from these sites. The misconduct

involved unauthorized and untrained personnel completing data forms at these two sites; the forms were then signed by the trained site staff. As a result, enrollment was terminated at these two sites and the data from the sites (n=67) were not used in the analysis.

The pre-specified demographic quotas were met and exceeded. The eligible population included between 54 and 59 subjects of each age between 12 and 17 years of age (see Table 1). Among the eligible population, 21% were Hispanic, 26% were African Americans, 42% were low literacy (defined as a REALM-Teen score of 58 or lower), and 7% reported previous use of emergency contraceptive pills.

Table 1. Eligible Population by Age Group

Age	N
12	54
13	56
14	54
15	59
16	57
17	55
Total	335

Source: derived by reviewer from applicant's final study report, Table 2.1a

Table 2 summarizes the understanding of the key concepts by the entire study population. At least 82.7% of subjects understood each of the six concepts. The least well understood concept was that Plan B One-Step should be taken as soon as possible after sex (82.7%).

Table 2. Study Subjects Understanding of Key Concepts

Key Concepts	Subjects who understand n (%) N=335
1. Plan B One-Step is indicated for prevention of pregnancy after unprotected sex	300 (89.6%)
2. Plan B One-Step should be taken as soon as possible after sex	277 (82.7%)
3. Plan B One-Step does not prevent sexually transmitted diseases or HIV/AIDS	310 (92.5%)
4. Plan B One-Step should not be used in place of regular contraception	309 (92.2%)
5. Plan B One-Step should be taken within 72 hours after sex	319 (95.2%)
6. Plan B One-Step should not be used by women who are already pregnant	320 (95.5%)

Source: derived by reviewer from applicant's final study report, section 10.2.3

The applicant performed a variety of exploratory subgroup analyses by demographic characteristic and by question. The subgroup analyses related to enrollment quotas are summarized in the tables that follow.

Table 3 summarizes the understanding of key concepts by age. Overall, the understanding of key concepts was similar from 12 to 17 years of age. Key concept #2, related to timing of pill ingestion, trends to being less well understood by the youngest subjects; however, these subjects appeared to understand key concept #5, also related to timing of pill intake, as well as the older subjects.

Table 3. Understanding of Key Concepts by Age, Primary Eligible Population

	Age					
	12 N= 54 %	13 N= 56 %	14 N= 54 %	15 N= 59 %	16 N=57 %	17 N=55 %
1. Plan B One-Step is indicated for prevention of pregnancy after unprotected sex	87	82	85	95	91	96
2. Plan B One-Step should be taken as soon as possible after sex.	78	77	83	88	83	87
3. Plan B One-Step does not prevent STDs or HIV/AIDS	91	88	87	98	95	96
4. Plan B One-Step should not be used in place of regular contraception	93	88	91	93	93	96
5. Plan B One-Step should be taken within 72 hours after sex.	98	89	89	98	98	98
6. Plan B One-Step should not be used by women who are already pregnant	94	95	91	98	97	98

Source: derived by reviewer from applicant's table 5.1.d, p. 124, final study report for LCS

Regarding race (Table 4), Whites trended toward understanding the key concepts somewhat better than African Americans and Others. Hispanic ethnicity did not seem to impact label comprehension, except possibly for a trend toward greater understanding of key concept #2 among Hispanics (Table 5). Lower literate subjects trended toward less understanding of all six key concepts (Table 6), and prior users of ECs tended to have somewhat better comprehension of key concepts than subjects who had never used ECs (Table 7).

Table 4. Understanding of Key Concepts by Race, Primary Eligible Population

	White only	Race African American	Other
	N= 163	N= 88	N=74
	%	%	%
1. Plan B One-Step is indicated for prevention of pregnancy after unprotected sex	95	88	89
2. Plan B One-Step should be taken as soon as possible after sex.	90	73	87
3. Plan B One-Step does not prevent sexually transmitted diseases or HIV/AIDS.	97	91	92
4. Plan B One-Step should not be used in place of regular contraception	97	90	92
5. Plan B One-Step should be taken within 72 hours after sex.	98	94	100
6. Plan B One-Step should not be used by women who are already pregnant	98	98	96

Source: derived by reviewer from applicant's Table 5.1c, p. 125 of final study report for LCS

Table 5. Understanding of Key Concepts by Ethnicity, Primary Eligible Population

	Hispanic	Non-Hispanic
	N= 70	N= 254
	%	%
1. Plan B One-Step is indicated for prevention of pregnancy after unprotected sex	93	92
2. Plan B One-Step should be taken as soon as possible after sex.	93	83
3. Plan B One-Step does not prevent STDs or HIV/AIDS	94	95
4. Plan B One-Step should not be used in place of regular contraception	93	94
5. Plan B One-Step should be taken within 72 hours after sex.	100	97
6. Plan B One-Step should not be used by women who are already pregnant	97	98

Source: derived by reviewer from Table 5.1f, p 126 final study report for LCS

Table 6. Understanding of Key Concepts by Literacy Level, Primary Eligible Population

	Literacy Level	
	7th grade or lower N= 140 %	8 th grade or higher N= 195 %
1. Plan B One-Step is indicated for prevention of pregnancy after unprotected sex	82	95
2. Plan B One-Step should be taken as soon as possible after sex.	74	89
3. Plan B One-Step does not prevent STDs or HIV/AIDS	84	99
4. Plan B One-Step should not be used in place of regular contraception	87	96
5. Plan B One-Step should be taken within 72 hours after sex.	92	97
6. Plan B One-Step should not be used by women who are already pregnant	92	98

Source: derived by reviewer from applicant's Table 5.1.g, p. 127 of final study report for LCS

Table 7. Understanding of Key Concepts by Ever Use of Emergency Contraceptive Pills, Primary Eligible Population

	Prior use N= 24 %	Never used N= 311 %
	1. Plan B One-Step is indicated for prevention of pregnancy after unprotected sex	100
2. Plan B One-Step should be taken as soon as possible after sex.	83	83
3. Plan B One-Step does not prevent sexually transmitted diseases or HIV/AIDS	100	92
4. Plan B One-Step should not be used in place of regular contraception	96	92
5. Plan B One-Step should be taken within 72 hours after sex.	100	95
6. Plan B One-Step should not be used by women who are already pregnant	100	95

Source: derived by reviewer from applicant's Table 5.1h, p. 128 of final study report for LCS

The applicant also provided a historical comparison between this LCS and the LCS done in 2001 for Plan B (see Appendix 8 of the final study report). The 2001 study included 656 subjects from 12 to 50 years old, most of whom (n=580) were 17 years and older. The 2001 study was of similar design and 13 questions in both studies overlapped. The proportions of subjects who answered correctly were similar for 11 of 13 questions. In the two questions with the greatest difference between groups, the older study had a greater percentage of incorrect responses. Both of these questions were related to the instruction to take the tablets as soon as possible after sex.

Comments: The social science reviewer commented that the study demonstrated that adolescents were able to understand the key elements of labeling; I concur.

The applicant followed the advice of the FDA regarding the design and conduct of the LCS. Overall, the understanding of labeling was acceptable. The younger teens trended toward having a lower understanding of one element related to dose timing (“as soon as possible”) but had a similar understanding of a second element related to dose timing (“within 72 hours”) compared with older teens. Whether the findings of the subgroup analyses represent chance variation related to exploratory analyses is unknown; however, I do not expect the findings to be of clinical significance. As subjects understood that the product should be taken within 72 hours after sex, efficacy should be acceptable.

It is important to note that one of the questions testing the second element (“as soon as possible”) was ambiguous and may have contributed to the lower overall understanding of the element compared with the other five elements (see social science review.) With the caveat that cross-study comparisons have pitfalls, historical data from a similar study for Plan B found a greater percentage of generally older subjects had a lower understanding of element 2 (“as soon as possible”) than the younger subjects in the Plan B One-Step study.

That OTC access may shorten the time interval between a contraceptive failure and use of Plan B One-Step is self-evident; obtaining an OTC drug requires only a trip to the pharmacy, whereas obtaining a prescription typically requires contacting a healthcare provider, an appointment to obtain a prescription, and a trip to the pharmacy. It can be difficult for this to all occur within 72 hours. OTC access may therefore improve efficacy for young teenagers who currently must have a prescription to purchase Plan B One-Step.

The comprehension of key elements in this LCS is akin to the numbers seen in LCS studies that have supported approval of other OTC products. It is typical for low literacy numbers to be less robust than those of the general population. The numbers for subjects of low literacy are not atypical and are acceptable.

An LCS identifies elements of labeling that are not adequately understood, and this Plan B One-Step LCS showed that the tested elements of labeling were adequately understood by the various subgroups assessed. However, an LCS does not test consumer behavior because participants in an LCS study are not seeking to use the product. In addition, the design of a LCS may impact the way subjects interact with labeling. Actual consumer behavior can be evaluated in an actual use study (AUS). For this proposed OTC switch, the applicant performed an AUS, which is summarized in the following section.

8.2 Actual Use Study (DR-LEV-302)

The actual use study (AUS) is reviewed in detail in Dr. Chang’s primary clinical review. I have read Dr. Chang’s review and agree that the results of the AUS support that adolescents can appropriately and safely use Plan B One-Step in an OTC setting. Dr. Chang recommended approval of the application pending satisfactory negotiation of labeling. Dr. Izem performed a statistical review of the AUS and was able to reproduce the applicant’s findings for the primary endpoints from the study datasets. A brief summary of the AUS follows.

AUS Study Design and Objectives:

The AUS was an open-label, single-arm, naturalistic study to determine the percentage of subjects who correctly self-select and use Plan B One-Step under simulated OTC conditions. The study sought to enroll subjects 11 to 17 years old who were seeking emergency contraception (EC).

Each subject read the label without assistance. The study product was dispensed only to those subjects who appropriately self-selected and agreed to participate. Follow-up occurred at one, four, and eight weeks. Subjects were asked about product use, health problems since last contact, and pregnancy status. Subjects were also asked about repeated use of EC since enrollment, and charts were evaluated for repeat use as well. Sample size was negotiated with FDA and ultimately the study was to include a minimum of 25 females of each age, 14 through 17 years, and any subjects from 11 to 13 years who were eligible to participate. The originally agreed-upon number of subjects in the 11- to 13-year age range was 25, but, after two years of study experience, enrollment in that age range was minimal. FDA agreed to a protocol amendment to continue to enroll 11- to 13-year olds without a minimum number of enrollees after the applicant presented their interim enrollment data and provided literature showing that difficulty enrolling younger subjects was to be expected. When Plan B One-Step was approved in July 2009 as an OTC product for women 17 years of age and older, the AUS protocol was amended to no longer recruit 17-year-olds.

The co-primary objectives of the study were to determine the percentage of subjects who appropriately self-selected and the proportion of subjects who correctly used Plan B One-Step under simulated OTC conditions. Correct self-selection was defined as wanting to use the product for its indication AND not having an allergy to levonorgestrel, a positive pregnancy test, or a known pregnancy. Correct use was defined as taking Plan B One-Step within 72 hours following unprotected sex.

The secondary objectives were to estimate the incidence of adverse events and repeat use of emergency contraception during the 8-week follow-up period. Adverse events were captured at regularly scheduled telephone contacts or return visits by asking if the subject had had any health issue since the last contact.

AUS Study Results:

A total of 343 subjects were enrolled in the AUS. Table 8 shows the age range of enrolled subjects. Clinics were unable to enroll any subjects younger than 13 years of age because no subjects in this age range presented for emergency contraception. The race distribution was 42.9% Latina, 19.8% Asian/Pacific Islanders, 14.0% African-American, and 11.4% White.

Approximately 40% of subjects had used EC previously, with the percentage increasing with age (ranging from 0% of 13-year-olds, to 66.2% of 17-year-olds). Approximately 29.4% of subjects reported no previous use of contraception with the percentage decreasing by age (66.7% of 13-year-olds, to 15.4% of 17-year-olds). Approximately 88.3% had never been

pregnant, with the percentage decreasing with increasing age (100% of 13 year olds to 81.5% of 17 year olds).

Table 8. Number of Subjects and Prior Use of Contraception by Age in AUS

Age of Subjects	13 years old	14 years old	15 years old	16 years old	17 years old
N	3	35	100	140	65
No previous use of contraception	66.7%	51.4%	31%	28.6%	15.4%

Source: Applicant's Submission, Clinical Study Report, Table 8

By the applicant's analysis, results of the primary objectives for the enrolled population were:

- 90.1% appropriately self-selected
- 88.6% of those who appropriately self-selected correctly used the product within 72 hours of intercourse

Comment: Most teens were able to correctly self-select, and among those who correctly self-selected, most also correctly used the product.

The primary clinical review by Dr. Chang contains a detailed analysis of reasons for inappropriate selection and use, and the expected consequences. Dr. Chang noted that the applicant's definitions were conservative, particularly when the clinical consequences are considered. For example, the most common reason that resulted in being coded as an inappropriate self-selector was "might be pregnant." (25 of 34 adolescents); however, subsequent responses suggested that many thought they "might be pregnant" only because they had had unprotected sex. In Dr. Chang's review, she considered only two subjects as inappropriate self-selectors because they had positive pregnancy tests at the time of self-selection. It is worth noting that although these two subjects would derive no benefit from the use of Plan B One-Step, the risks (for example, nausea) are minor.

Similarly, Dr. Chang's analysis of the reasons for being coded as an incorrect user showed that the applicant's definition of incorrect use was conservative. By exploring the datasets, Dr. Chang found that the applicant coded eleven subjects as incorrect users because the subjects did not follow-up within 10 days of the clinic visit; however, these eleven subjects used Plan B One-Step correctly (that is, within 72 hours of the index episode of unprotected sex.) Excluding these subjects from the "incorrect user" population produces gives a correct use percentage of 92.3%. This is very close to the findings of the AUS study conducted to support the OTC switch of Plan B, where 92.4% of subjects took the first dose of Plan B within 72 hours of unprotected intercourse. I have considered Dr. Chang's analysis and agree that the study has demonstrated acceptable use of Plan B One-Step by teens.

Table 9 and Table 10 show exploratory analyses of the primary endpoint by age. Overall, there are no clear trends by age.

Table 9. Proportion of Enrolled Population that Appropriately Self-Selected by Age (Years)

	13	14	15	16	17
Number of Subjects	3	35	100	140	65
Appropriate Self-Selection	2 (66.7%)	30 (85.7%)	91 (91.0%)	128 (91.4%)	58 (89.2%)

Source: Applicant's Submission, Clinical Study Report, Table 18

Table 10. Proportion of Treated Population Demonstrating Correct Product Use within 72 Hours after Intercourse by Age (Years)

	13	14	15	16	17
Number of Subjects	1	30	87	123	56
Product Use within 72 Hours	1(100%)	24 (80.0%)	78 (89.7%)	107 (87.0%)	53 (94.6%)

Source: Applicant's Submission, Clinical Study Report, Table 19

Comments: Results support that the large majority of teens can use OTC labeling to appropriately self-select and use Plan B One-Step. There was no clear trend in proportion of correct self-selection or correct use by age, although more older teens than younger teens sought to use Plan B One-Step. (The drop-off in number of enrollees at age 17 was the result of a protocol amendment that stopped recruitment of 17-year-olds after Plan B One-Step was approved as an OTC product for women 17 years of age and older.) The trend of greater use of contraception with age is consistent with my own experience as an obstetrician/gynecologist in clinical practice.

A secondary objective was measuring the repeat use of emergency contraception during the 8-week follow-up period. Most subjects reported a single use of Plan B One-Step during the study. Table 11 summarizes a subgroup analysis by age. There was no discernable trend for repeat use by age. Repeat use included one additional time (13.0%), two additional times (5.4%), or three additional times (0.7%).

Table 11. Repeat Product Use in the Completed Follow-Up Population (N=277) by Age (Years) at Screening

Number of repeat uses	13	14	15	16	17
None	1 (100%)	22 (84.6%)	64 (78.1%)	92 (81.4%)	45 (81.8%)
1	0	1	12	19	6
2	0	3	6	3	4
3	0	0	1	1	0

Source: Applicant's Submission, Clinical Study Report, Table 28

Comment: Most teens did not repeat use during the 8-week follow-up period and there was no trend for repeat use by age. None of the teens used Plan B One-Step more than 3 times in 8 weeks.

The analysis of repeat use adequately addressed Dr. Galson's concern that teens might substitute the product for routine and more effective contraception. I do not, however, agree with Dr. Galson's concern. It is not within FDA's purview to require that a person use the most effective birth control method available (or, for that matter, the most effective

antihypertensive or heartburn drug available). Condoms are not the most effective contraceptives, but FDA does not restrict access to condoms because condoms may be substituted for more effective methods. It is also not within the FDA’s purview to require that routine contraception be used by sexually active people. The decision to use birth control and the choice of birth control method depend on many factors (sexual frequency, level of concern about pregnancy, price, access, concern about sexually-transmissible infection, contraindication to a particular method, to name just a few.) For the youngest teens in the study, most had used no contraception in the past. Use of Plan B One-Step once or intermittently can be a reasonable choice.

The other secondary objective was to estimate the incidence of adverse events. There were no deaths and one serious adverse event was reported (a miscarriage). Miscarriage is a common outcome of pregnancy and there is no evidence that progestins are causally related to miscarriage. Other adverse events were reported infrequently and no unexpected adverse events occurred. Without a control group to provide a background frequency for the reported adverse event, the contribution of drug to the adverse events reported is unclear; however, there were no worrisome or unexpected findings. The most frequently reported adverse events were nausea, headache, and menstrual irregularity.

Table 12. Frequency of Reported Adverse Events in $\geq 1\%$ of the Safety Population: Subjects Who Reported Any Use of Plan B One-Step

Adverse Event (MedDRA Preferred Term)	Total Number of Subjects = 299 N (%)
Nausea	8 (2.7%)
Headache	8 (2.7%)
Menstruation Irregular	6 (2.0%)
Vaginal Bleeding*	4 (1.3%)
Pelvic Pain	4 (1.3%)
Influenza	3 (1.0%)
Vulvovaginal Mycotic Infection	3 (1.0%)
Vaginal Spotting*	3 (1.0%)
Dizziness	3 (1.0%)
Abdominal Pain Upper	3 (1.0%)
Fatigue	3 (1.0%)
Vomiting	3 (1.0%)

*Vaginal Bleeding, regardless of severity, codes in MedDRA to a Preferred Term of “Vaginal Haemorrhage.” Therefore, for clarity, the applicant used the MedDRA Lower Level Term rather than the Preferred Term
 Source: Applicant’s Submission, Clinical Study Report, Table 29

Subjects reported seven pregnancies, only one of which was reported by investigators as an adverse event. The pregnancy data are summarized in Table 13.

Table 13. Summary of Pregnancies

Site/Subject	Age (Years)	Used Plan B within 72 hours of unprotected intercourse	Comments	Outcome
1/0107	16	Yes (one day after unprotected sex)	By 8-week ultrasound, conceived on or shortly after the index episode of unprotected sex	Surgical termination
1/0131	14	Yes (one day after episode of unprotected sex for which she presented to the clinic)	By 13-week ultrasound, was about 1 week pregnant when she took Plan B-One Step (too early for self-diagnosis or positive pregnancy test)	Surgical termination
1/0302	17	Yes (two days after unprotected sex)	By 7-week ultrasound, conceived shortly after the index episode of unprotected sex.	Surgical termination
1/0362	16	Yes (two days after unprotected sex)	By 7-week ultrasound, conceived on or shortly after the index episode of unprotected sex.	Surgical termination
1/0384	16	Yes (one day after unprotected sex)	By 26-week ultrasound, conceived after the index episode of unprotected sex	Delivered healthy infant at 36.5 weeks gestation
1/0405	16	Yes (one day after unprotected sex)	By 7-week ultrasound, conceived on or shortly after the index episode of unprotected sex	Ongoing pregnancy
1/0502	16	Yes (one day after unprotected sex)	Negative pregnancy test two weeks after taking Plan B One-Step; positive 3 weeks after taking Plan B One-Step; therefore, likely conceived after the index episode of unprotected sex.	Miscarriage

Source: Derived by reviewer from pregnancy narratives and review of case report forms in Applicant's submission, Clinical Study Report

Comments: The pregnancy data do not support a relationship of age to lack of efficacy. The pregnancy data also do not support a lack of efficacy related to inappropriate use. By ultrasound dating, one young woman may have been pregnant when she took Plan B One-Step, but she was too early in gestation (1 week post conception) to have missed a period and suspected pregnancy. Her use of Plan B One-Step was therefore appropriate. All women who became pregnant used Plan B One-Step as directed on the OTC labeling. Some pregnancies are expected to occur despite correct use: Plan B One-Step reduces, but does not eliminate, the chance of pregnancy after unprotected sex. In clinical trials, approximately 84% of expected pregnancies were prevented.

At the time the clinical study report was finalized, 12 subjects had not completed all three follow-up contacts; however, their drug usage information was available when the clinical study report was finalized. The applicant provided their follow-up information in the 120-day

safety update submitted during the review cycle. No adverse events and no additional drug usage were reported for the 12 subjects.

8.3 Postmarketing Spontaneous Reports

Of 69 countries in which levonorgestrel 1.5 mg is legally marketed, 32 market the product as an OTC drug. There have been no regulatory or marketing authorization actions taken for safety reasons, and the product has not been withdrawn from or restricted in any market for safety reasons. Between Jul-09 and Jan-11, approximately [REDACTED]^{(b) (4)} tablets of Plan B One-Step were distributed in the United States.

The applicant provided summaries of postmarketing reports from three databases:

- Teva's internal database (10-Jul-2009 through 30-Nov-2010)
- The World Health Organization (WHO) database (10-Jul-2009 through 15-Feb-2011)
- The FDA's AERS database (10-Jul-2009 through 30-Sep-2010)

Contents of these three databases are expected to overlap considerably because of regulatory reporting requirements; the databases contain foreign reports as well as U.S. reports.

The applicant also provided a 120-day safety update during the review cycle; the safety update referred to the periodic adverse drug experience report (PADER) for the reporting period of 1-Jan-2011 to 31-Mar-2011. The applicant was not conducting any clinical trials at the time the update was submitted.

Abuse potential is an important consideration when deciding whether a drug should be OTC. There is no evidence in its long marketing history that levonorgestrel is a drug with abuse or even overuse potential. Levonorgestrel is not known to have any stimulant pharmacologic properties. According to the current package insert, "there are no data on overdosage with Plan B One-Step, although the common adverse event of nausea and associated vomiting may be anticipated." The fact that the product packaging contains only one pill presents a practical barrier to impulsive overdosing. The fact that an overdose leads to unpleasant effects (nausea and vomiting) makes it highly unlikely that levonorgestrel will ever be a popular drug of abuse. The applicant's preliminary review of the databases from the Drug Abuse Warning Network (DAWN) and the American Association of Poison Control Centers (AAPCC) indicated that there was no meaningful information present. The analysis of the DAWN database for 2004-2009 indicated there were no DAWN reports for contraceptives during that time. Under the category "progestins," a rate of 0.1 cases per 100,000 population was reported for 2008, and no cases were reported for 2004-2007 or 2009. The analysis of the AAPCC database for 2008 and 2009 did not detect a signal for poisoning potential.

Comment: Based on a long history of safe use, lack of stimulant effect, the single-dose packaging, and the fact that vomiting occurs with higher doses, the likelihood of abuse or overuse of levonorgestrel is remote (and has not been demonstrated.)

Analysis of the postmarketing databases did not detect any new or unexpected safety signals; there was also no evidence of unique safety issues in younger teens. A brief summary of the postmarketing data by database follows.

Applicant's Internal Database

The applicant reviewed the internal postmarketing safety database for Plan B One-Step from the time of approval on July 10, 2009 through Nov 30, 2010. The search included the age range of 9 to 16 years. The youngest reporter was 13 years old. There were 332 events reported by 186 users, representing 2.4% of all events reported for the time period. The pattern of events did not show any additional risk in the younger population. One subject reported a serious, unlabelled event: vomiting blood (hematemesis). The most frequently reported adverse events for the 9-year to 16-year age range were:

- Menstruation irregular (n=106)
- Pelvic pain (n=25)
- Vomiting (n=24)
- Nausea (n=22)
- Menstruation delayed (n=19)
- Abdominal pain (n=18)
- Headache (n=18)

For comparison, the applicant tabulated all adverse events, regardless of age, over the same time period. The most frequently reported adverse events were:

- Menstruation irregular (n=4959)
- Pelvic pain (n=955)
- Vomiting (n=628)
- Nausea (n=940)
- Menstruation delayed (n=546)
- Abdominal pain (n=513)
- Headache (n=440)

Comment: The most commonly reported adverse events were the same for younger teens compared with all women. Menstrual irregularity was the most commonly reported adverse event, regardless of age.

In the FDA 915 safety review of both Plan B and Plan B One-Step, 18 cases of hematemesis, 4 of which occurred in users of Plan B One-Step, were detected in the FDA's AERS database between Jul 2007 through Dec 2010. (See Additional FDA Analysis of Postmarketing Data, below.) None of the cases were reported by healthcare providers, and details were scant. Most cases (12) were described as mild; 3 were described as severe (1 in a woman with leukemia); 3 were not rated. No age-clustering was noted. As hematemesis can occur as a complication of vomiting, a known adverse effect, it is not surprising that occasional reports of hematemesis occur. The 915 reviewers (from the Office of Surveillance and Epidemiology and the Division of Reproductive and Urologic Products) did not view the cases as a significant signal; I concur.

WHO Database

The applicant requested a search of the WHO VigiBase for reports for levonorgestrel 1.5. mg from 10-Jul-2009 through 15-Feb-2011. A total of 369 cases reporting 969 events were obtained. Among these 369 cases, 5 were in women aged 16 and under. Two of these were also in the AERS database. The remaining three reports were of breast disorder, ectopic pregnancy, and fetal abnormality (not otherwise specified).

Comment: Information from the WHO VigiBase was limited but did not detect any age-specific adverse events.

AERS Database

The applicant conducted a search of the AERS database from July 10, 2009 to 30-Sep-2010 for Plan B, Plan B One-Step, and other levonorgestrel-containing emergency contraceptive products (ECs).

For women of all ages, there were 71 cases reporting 303 adverse events for Plan B and Plan B One-Step, and an additional 28 cases reporting 66 adverse events for other levonorgestrel ECs. A total of four cases were identified in young women aged 16 and under; all reporters were 15 or 16 years of age. The four cases reported hypersensitivity-type reaction, menstrual changes, emotional distress, lack of efficacy, nausea, vomiting, and hematemesis. These events have also been reported in the older population.

Comment: Analysis of the AERS database did not reveal any age-specific safety issues.

120-Day Safety Update

The applicant was not conducting any clinical trials during the update period. There were no reports from research sites regarding any subject experiencing a serious adverse event in the AUS. A quarterly periodic adverse drug experience report (PADER) covering 1-Jan-2011 through 31-Mar-2011 did not detect any signal suggesting a change in the safety profile of Plan B One-Step or any age-specific safety issues.

Additional FDA Analysis of Postmarketing Data

During the course of the review, FDA performed a 915 review of Plan B One-Step. A 915 review occurs routinely 18 months after approval and exposure of at least 10,000 patients, whichever is later. The review entails a detailed look at postmarketing data by FDA's Office of Surveillance and Epidemiology and the Office of New Drugs, Division of Reproductive and Urologic Products. The 915 review evaluated reports received for Plan B One-Step from the time of approval through 31-Jan-2011. The reviewers concluded that "No potential safety issues were identified in this review that would warrant any labeling changes or changes in the product's safety profile."

I searched FDA's document tracking system ("DARRTS") on 7/5/2011 for open safety issues for levonorgestrel or Plan B One-Step and found none.

Comments: The analysis of postmarketing data did not detect any new safety issues. Teens experienced a similar profile of adverse events compared with all women.

8.4 Literature

The applicant reviewed the published literature for EC use and provided references. The primary clinical reviewer, Dr. Christina Chang, analyzed the references provided by the applicant and performed an independent literature review. Review of the literature did not detect any new safety issues or safety issues specific to younger women. For details, see Dr. Chang's primary clinical review.

7. Advisory Committee Meeting

An Advisory Committee meeting was unnecessary for the present submission because an Advisory Committee has already deliberated on the topic of OTC availability for Plan B in 2003. That joint Advisory Committee (Reproductive Health Drugs and Nonprescription Drugs) met to discuss the proposed switch of Plan B from Rx-to-OTC status. The joint Advisory Committee recommended by a vote of 23 to 4 that Plan B be switched to OTC availability without age restriction. As Plan B and Plan B One-Step are nearly identical (except that the Plan B One-Step dosing regimen is simpler), the review team decided there was no need to convene another Advisory Committee meeting on the same topic.

8. Pediatrics

The application did not trigger the Pediatric Research Equity Act because it did not propose a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

Dr. Lisa Mathis, Director of CDER's Pediatric and Maternal Health Staff, provided a consult review for this sNDA. Dr. Mathis concluded that the applicant has fully responded to the data needs as outlined in Dr. Galson's memos and that the studies demonstrated that women of child bearing potential of all ages can appropriately self-diagnose and administer Plan B One-Step in an OTC setting. Dr. Mathis recommended approval of the application.

9. Other Relevant Regulatory Issues

The review team requested a routine audit of the AUS study. Because the University of California, San Francisco site enrolled the majority of subjects (316 of 343 subjects), the review team selected the site for audit. The AUS study passed FDA audit: FDA's Office of

Scientific Investigations (OSI) concluded that the study was “conducted adequately and the data in support of the NDA appear reliable. OSI issued a “no action indicated” recommendation.

The applicant certified to not using the services of any person debarred under section 306 of the F, D, and C Act in connection with the application. The applicant also provided a signed certification of financial interests (Form 3454) stating that there were no financial conflicts of interest for the investigators and subinvestigators involved in the clinical study DR-LEV-302. The patent form (Form 3542a) stated that there are no relevant patents that claim the drug substance, drug product, or method of use.

10. Labeling

Only highlights of labeling appear in this review. For details of labeling, please see the reviews by Maria Ysern from the Division of Nonprescription Regulation Development.

The applicant proposed a number of changes to the already approved OTC labeling:

- Removal of the words “Rx only for women younger than age 17” from the principal display panel (PDP), and removal of the labeling by age from the Directions section of Drug Facts. These changes were acceptable to the review team and supported by the data in the submission.
- Addition of claim (b) (4) on the PDP. (b) (4)
The statement was not supported and was therefore unacceptable to the review team.
- Removal of redundant text from the consumer information leaflet; deletion of redundant text was generally acceptable to the review team.
- Replacement of “One tablet. One dose.” with (b) (4) on the PDP. The team recommended retaining the current language because the new language was not tested and there were various possible interpretations.
- Addition of the statement (b) (4) This addition was not acceptable to the review team. (b) (4)

The proprietary name was unchanged.

With removal of labeling by age, the labeling no longer has gender-specific text. While it is unlikely that men would use the product, it is reasonable to note on the label that the product is for women. I recommend adding “For women only” to the Directions section to replace the current text in Directions that says “women 17 years of age or older.”

Labeling comments were sent to the applicant. On October 21, 2011, the applicant responded with labeling revisions that addressed all but one of FDA’s concerns: removal of the claim (b) (4)

The review team did

not agree with the claim. [REDACTED]

(b) (4)

[REDACTED] When this review was finalized, a second labeling review to support the next round of labeling negotiations was underway.

11. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend approval of the application pending satisfactory negotiation of labeling.

- Risk Benefit Assessment

FDA approved Plan B One-Step for all women of reproductive age based on its safety and efficacy. The applicant does not seek changes in the product, its indication, the dosing regimen, or the population for whom it is indicated. The submission is limited to a proposal to change the marketing status from prescription to over-the-counter (Rx-to-OTC) for women younger than 17 years; therefore, the risk-benefit assessment focuses on the ability of younger teens to use Plan B One-Step with OTC labeling. Plan B One-Step is already marketed OTC for women who are 17 years and older.

The data from the actual use study (AUS) and label comprehension study (LCS) support that teenagers can safely and effectively use Plan B One-Step in an OTC setting. The LCS and the AUS satisfactorily addressed Dr. Galson's call for more consumer data in younger teens. The LCS study enrolled 335 young women between the ages of 12 and 17; the AUS study enrolled 343 young women between the ages of 13 and 17. Neither study detected any clinically important variation in use of the OTC labeling for Plan B One-Step with age. None of seven pregnancies reported in the AUS were the result of incorrect use of Plan B One-Step. There were no reports of unexpected adverse events in the AUS.

The applicant provided reviews of postmarketing reports and the scientific literature, and the primary clinical reviewer performed an independent review of the scientific literature. The reviews did not reveal any age-specific issues or new safety signals.

Condoms and spermicides provide a long-time precedent for OTC access to contraception regardless of age. Condoms are available OTC for anyone to purchase, and condoms may certainly be purchased by teenagers. Spermicides are similarly available OTC without age restrictions. Approval of this supplement will make labeling for Plan B One-Step consistent with labeling of other OTC contraceptives by removing the age restriction and providing the same label to all for whom the product is indicated.

The "OTC-ness" of Plan B One-Step is clear: the condition, unprotected sex, can be readily self-diagnosed and safely self-treated. Self-diagnosis requires that a woman realize that she has had unprotected sex. Self-treatment requires taking a single tablet within 72 hours of this realization. The only "do not use" conditions are allergy or pregnancy, and OTC products

have been successfully labeled with allergy and pregnancy warnings for decades. For Plan B One-Step, the pregnancy contraindication exists because the product is ineffective if a woman is already pregnant; however, there are no known risks to the pregnancy if a woman who is pregnant takes levonorgestrel. The active ingredient in Plan B One-Step is not a drug of abuse. OTC labeling for Plan B One-Step is simple compared with, for example, labeling of OTC products such as analgesics or heartburn therapies, all of which may be purchased and used by teens.

The submission adequately addressed Dr. Galson's concerns by providing data in younger women to support their ability to use Plan B One-Step with the aid of an OTC "Drug Facts" label.

I recommend that OTC access to Plan B One-Step be extended to all women of reproductive age.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None; standard postmarketing pharmacovigilance is appropriate

- Recommendation for other Postmarketing Requirements and Commitments

None

- Recommended Comments to Applicant

None

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/s/

LESLEYANNE A FURLONG
10/25/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021998/S-002

MEDICAL REVIEW(S)



MEDICAL OFFICER'S MEMORANDUM

Department of Health and Human Services
Food and Drugs Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation (HFD-560)

NDA #: 21-998/S-002
Document: Amendment to the Complete Response, Submitted on March 9, 2012

Applicant: Teva Women's Health, Inc. (Teva)

Drug: Plan B One-Step, Levonorgestrel Tablets (1.5 mg)

Indications: Emergency Contraception

Submission Date: March 13, 2013

Review Date: March 27, 2013

Reviewer: Christina Chang, M.D., M.P.H.
Team Leader: Lesley-Anne Furlong, M.D.

1. INTRODUCTION

This is an addendum to the DNCE medical officer's review¹ for the Complete Response (CR) from Teva seeking to market Plan B One-Step over-the-counter (OTC) to women and adolescents aged 15 years and older. Plan B One-Step was first approved on July 10, 2009 for dual marketing, allowing it to be available without prescription to women aged 17 years and older. Access to Plan B One-Step for adolescents aged 16 years and younger is by prescription only.

On February 7, 2010, the applicant sought to eliminate dual marketing status with the submission of supplement-002, which provides for full OTC access to Plan B One-Step without age restriction. Following the CR action taken by FDA on December 7, 2011, the applicant submitted a CR on March 9, 2012, requesting to only expand OTC marketing to adolescents aged 15 and 16 years.

¹ Medical Officer's Review for NDA 21-998/S002 of the submission dated March 9, 2012. The review was signed by the primary medical reviewer on May 19, 2012 and finalized by the clinical team leader in DARRTS on May 20, 2012.

In the current amendment to the March 9, 2012 CR, the applicant continues to seek OTC access for 15- and 16-year-olds. The amendment proposes no new labeling and provides no new clinical data. The amendment does include a new proposal for tertiary packaging, an educational campaign, a postmarketing monitoring program, and a commitment to submit prescription (Rx) labeling for Plan B One-Step to be marketed in adolescents aged 14 years and younger.

2. BACKGROUND

The regulatory history for Plan B One-Step and its predecessor (Plan B, two doses of levonorgestrel 0.75 mg tablet taken 12 hours apart) is complex and documented in detail elsewhere.² The regulatory history is abbreviated chronologically below:

- July 28, 1999: Plan B was approved for Rx marketing (NDA 21-045).
- January 24, 2006: NDA 21-998 for Plan B One-Step was submitted. The NDA proposed Rx access for Plan B One-Step.
- August 24, 2006: Under S-011 to NDA 21-045, Plan B was approved for OTC marketing for women aged 18 years and older. Access to Plan B for adolescents younger than 18 years would remain Rx only.
- November 22, 2006: NDA 21-998 was not approved, and the sponsor was directed to develop a dual packaging configuration for the product similar to Plan B.
- January 9, 2009: A Complete Response (CR) to the not approvable letter was submitted to NDA 21-998, proposing dual marketing status for Plan B One-Step, mirroring that for Plan B (i.e., OTC for women aged 18 years and older, Rx for adolescents younger than 18 years).
- March 23, 2009: A U.S. District Court Judge issued an order 1) directing FDA to permit the Plan B drug sponsor “to make Plan B available to 17-year-olds without a prescription; and (2) remanding to FDA for reconsideration “its decision regarding the Plan B switch to OTC use.”³
- June 11, 2009: Supplement S-015 was submitted to NDA 21-045, providing for OTC availability of Plan B for women aged 17 years and older and Rx availability for adolescents younger than 17 years (i.e., dropping the age for OTC availability from 18 to 17).
- July 10, 2009: NDA 21-998 for Plan B One-Step was approved for OTC marketing for women aged 17 years and older. NDA 21-045/Supplement S-015 for Plan B was also approved, ensuring consistency in the aged-based marketing status between Plan B and Plan B One-Step.
- February 7, 2011: Teva submitted an efficacy supplement (S-002) to NDA 21-998, seeking full OTC marketing status for Plan B One-Step (i.e., without lower age restriction), supported by new data from an actual use study in women younger than 17.
- December 7, 2011: HHS Secretary Sebelius directed CDER not to approve supplement S-002, citing lack of data in the “youngest adolescents.”
- March 9, 2012: Teva submitted a CR to S-002, seeking to market Plan B One-Step without prescription to females 15 years and older.

² Medical Officer Reviews for NDA 21-998, dated October 5, 2011 and May 19, 2012.

³ *Tummino v. Torti*, No. 05-CV0366 (ERK) (VVP), 603 F. Supp. 2d 519, 550 (E.D.N.Y. 2009) (Korman, J.).

- September 9, 2012: PDUFA goal date for the CR; no action on the CR has been taken to date.

3. REVIEW

This amendment, dated March 13, 2013, contains no changes to the core proposal submitted in the March 9, 2012 CR. No new clinical data or labeling revisions are included in this amendment. The submission describes four elements as “clarifying information” for or “modifications” to the proposal with respect to product packaging, distribution, and marketing. In the opinion of this medical officer, none of these elements alter the benefit/risk assessment regarding OTC marketing of Plan B One-Step, as documented in my previous reviews.²

These four elements are as follows:

1. Conditions of Distribution and Sale

The applicant commits to the following:

- Plan B One-Step will only be available at retail outlets with an on-site pharmacy. Therefore, the product will not be sold in convenience stores or gas stations.
- The product will be placed at the Family Planning or Female Health aisles in these outlets.
- Teva will contract only with retailers willing to adhere to these limitations.

Medical officer comment:

The first two items were already included in the March 9, 2012 CR submission. This updated proposal is acceptable.

2. Packaging

The product is packaged in a single-piece, box-wallet carton, with a tamper-evident tear strip; the single, 1.5 mg tablet of levonorgestrel is enclosed in a blister pack glued to this box wallet.

The amendment provides for the following theft-detering features:

- Radio-frequency and magnetic security tags that will trigger alerts in the retail outlet in the event of theft.
- The box wallet will be enclosed in a heavy gauge, clear, plastic “clamshell” similar to that used for other high-value products such as Abreva (docosanol cream for cold sore) and Nicorette (nicotine replacement therapy). The bulkiness of the package is thought to contribute to prevention of theft. Additionally, any attempt made to open the clamshell package to retrieve the product will be evident. The applicant implies that this protective feature has been requested by FDA, although the origin of this request is not stated in the submission.

Medical officer comment:

Given the current price points of Plan B One-Step (retail prices of one levonorgestrel tablet at over \$40), these theft-deterrent packaging features are reasonable.

3. Post-approval Education and Monitoring

If this supplement is approved, Teva notes their commitment to educate the consumers, pharmacy staff, and healthcare professionals on the differences between the new, unrestricted OTC status and previous dual marketing status. The education campaign will emphasize the following:

- That Plan B One-Step can be found in the Family Planning aisle rather than behind-the-counter;
- The product can be purchased without prescription by those 15 years and older;
- The product is not to be sold to those under 15 years of age;
- Age verification must be carried out at the point of sale.

Teva states that the FDA has requested a third party audit of retail outlets to assess compliance with the age-verification requirements – a “mystery shoppers” audit that is similar to one conducted under the former CARE (Convenient Access and Responsible Education) program for dual-labeled Plan B and Plan B One-Step. This third-party audit is intended to monitor pharmacy adherence to the requirement for age-based distribution. Teva proposes to conduct a single audit at 6 months post-launch, with the potential to conduct a follow-up audit 6 months later if significant non-compliance is identified in the first audit. If compliance is demonstrated in the first audit, the sponsor proposes to terminate CARE-like postmarketing monitoring responsibility.

Medical officer comment:

In a previous review dated July 8, 2009, I have already stated my opinion that the CARE program is not necessary to ensure safe use of Plan B One-Step. Furthermore, high compliance by pharmacies was already demonstrated by the applicant in a report submitted to FDA on June 1, 2012.⁴ Among the chain pharmacies surveyed, the audit found that 99.7% adhered with age verification requirement at the point of sale. Among non-chain, local pharmacies, the compliance rate was 91.4%. Therefore, the sponsor’s proposal to conduct a single mystery shopper audit is acceptable.

4. OTC Focus

In the March 9, 2012 CR submission, Teva acknowledged that if Plan B One-Step is made available to females 15 years and older without prescription and can be found on open pharmacy shelves subject to age-verification at the point of sale, there would not be a mechanism for access to the product by adolescents younger than 15. To mitigate this situation and maintain access to Plan B One-Step by this age group, Teva expressed its willingness to submit a separate supplement to the Division of Reproductive and Urologic Products (DRUP), within 90 days of the OTC approval, to seek Rx status for adolescents under 15 years of age. However, Teva notes that central to its willingness to do this are the following considerations:

⁴ Corrado JA, Stiffel P, Walsh M, Hummel A. Plan B as a Dual-Label Product. One-Year Update. U.S. Pharmacist December 2007. www.uspharmacist.com

- That timely review and action for the current S-002 supplement would not be affected by the planned Rx submission;
- Federal Trade Commission's (FTC) primary jurisdiction over the advertising for the OTC product would not be affected by the existence of the Rx product;
- The existence of the Rx product would not affect the determination of whether to grant exclusivity to the OTC product.

Medical officer comment:

The planned submission to maintain Rx access to adolescents under 15 is acceptable. It should be noted that generic versions of Plan B are currently available by prescription to adolescents under 17 years of age.

Of note, since the original approval of Plan B One-Step, the postmarketing safety profile of Plan B One-Step has been thoroughly reviewed. A total of 12 quarterly Periodic Adverse Drug Experience Reports (PADERs), containing data through June 30, 2012, have been submitted to FDA since the original approval. Review of data contained in these PADERs has not identified any new safety issue.⁵

4. CONCLUSIONS AND RECOMMENDATIONS

My opinion regarding this supplemental application remains unchanged: the benefit/risk determination remains in favor of OTC availability to ensure timely, unrestricted EC access for all post-menarchal adolescent females seeking to prevent unintended pregnancy. However, as stated in my review of the March 9, 2012 CR submission, I view this amended proposal as providing a significant improvement over current behind-the-counter access to Plan B One-Step by making the product available among family planning products on open pharmacy shelf space for females aged 15 years and over. Thus, I recommend an **Approval** action for this supplemental application (S-002).

⁵ Medical Officer Reviews for NDA 21-998, dated May 20, 2012 and September 4, 2012.

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/s/

CHRISTINA Y CHANG
04/05/2013

LESLEYANNE FURLONG
04/05/2013



MEDICAL OFFICER'S REVIEW

Department of Health and Human Services
Food and Drugs Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation (HFD-560)

NDA #: 21-998

Document: Postmarketing Periodic Adverse Drug Event Report (PADER)

Sponsor: Teva Women's Health, Inc. (Teva)

Drug: Plan B One-Step, Levonorgestrel Tablets (1.5 mg)

Indications: Emergency Contraception

Submission Date: July 31, 2012

Review Date: September 4, 2012

Reviewer: Christina Chang, M.D., M.P.H.

1. INTRODUCTION

This is a DNCE medical officer's review for the 12th quarterly PADER submitted by Teva since the 2009 approval of Plan B One-Step. Plan B One-Step is currently available without prescription to women aged 17 years and older; access to Plan B One-Step by adolescents aged 16 years and younger is by prescription only.

2. REVIEW

This safety report covered the period from April 1, 2012 to June 30, 2012. Teva summarized findings from 1,578 cases received during the reporting period. Of these 1,578 cases, 9 were identified by Teva as having serious outcomes; these warranted expedited 15-day reporting to FDA's Adverse Event Reporting System (AERS). Two of these nine cases included clinical information that had been medically confirmed; neither implicated levonorgestrel as the causative agent. The remaining 1,569 cases were associated with non-serious outcomes and were thus non-expedited reports. All non-expedited reports were of the spontaneous, consumer-generated nature and were not medically confirmed.

Nine individual cases reported adverse events meeting the regulatory definitions of serious outcomes. Two of these nine had already been reviewed elsewhere.¹ The remaining seven (three domestic, four foreign) represent new cases; a brief narrative of each case and discussion follow.

Case# 8586662 (foreign, ISR#s 8396420, 8423262, 8427715, and 8503218): This is a fatality involving a 22-year-old female (LMP unknown) with a significant history of hypersensitivity reactions (including anaphylaxis) to various food and penicillin. She took Levonelle (levonorgestrel 1.5 mg tablet) at lunch time on May 1, 2012. She reportedly experienced “nausea, dizziness and extreme tiredness” and felt worse with flu-like symptoms around 6 p.m. on May 1, 2012. The following day, May 2, 2012, she felt even worse, reportedly had increased temperature (precise temperature not given) and “swollen tonsils.” She attended a walk-in clinic where she was prescribed antibiotics, but reportedly she did not take the medication. Her condition deteriorated that by May 7, 2012 she had significant “left gland and left eye swelling,” a fever (39.9°C), and slurred speech. She was admitted to the hospital on [REDACTED] (b) (6) due to “feeling unwell, swollen eyes, and yellow drainage from her eyes.” An assessment by an otolaryngologist diagnosed left-sided tonsillar abscess.

She was transferred to the intensive care unit on the day of admission due to uncontrollable blood pressure from sepsis; a head/neck CT performed on [REDACTED] (b) (6) also revealed left internal jugular thrombosis, which was thought to have arisen from compression of blood flow by the abscess. Repeat head/neck CT demonstrated propagation of the left internal jugular venous clot with attenuation/spasm of both internal carotid arteries, and concurrent cavernous sinus thrombus. In addition, there was evidence of generalized hypoxic ischemic encephalopathy with diffuse cerebral sulcal effacement, loss of the normal grey/white matter differentiation, a bright cerebellum, and early cerebellar tonsillar descent. The patient was treated with high dose broad spectrum antibiotics for sepsis and tonsillar abscess. She was also on intermittent filter and heparin infusion for jugular vein thrombosis. Laboratory investigations performed on [REDACTED] (b) (6) [REDACTED] showed reduced a platelet count and elevated liver function tests. Cytomegalovirus (CMV) titers returned negative. Despite treatment, she developed multi-organ failure and died on [REDACTED] (b) (6). An autopsy confirmed the diagnosis of Lemierre’s syndrome secondary to peritonsillar abscess.

Medical officer comment:

Lemierre’s syndrome is characterized by disseminated abscesses and thrombophlebitis of the internal jugular vein after infection of the oropharynx. The constellation of the patient’s symptoms all could be attributed to untreated tonsillar abscess and subsequent development of sepsis. There is no evidence that levonorgestrel was causally related to the events described in this case. The close proximity in timing between ingestion of levonorgestrel and her illness is most likely coincidental. The sponsor assessed this case as not being related to levonorgestrel; I agree with Teva’s assessment.

¹ See this medical officer’s Clinical Review for the Complete Response to NDA 21-998/S-002, finalized in DARRTS on May 20, 2012. Four PADERS were included in this clinical review, covering the period from April 1, 2011 to March 31, 2012. This review identified no new safety issues.

Case# 8493795 (domestic, ISR#s 8259261 and 8261857): This is a spontaneous report from a friend of a consumer (age, LMP unknown) who took Plan B One-Step on March 31, 2012 for emergency contraception. Her medical history is significant for severe allergy to diphenhydramine and shellfish. The consumer reportedly experienced “lock jaw, uncontrollable shakes, slurred speech, leg pain and a possible allergic reaction on the day she took Plan B One-Step. This report was not medically confirmed and no further information is available.

Medical officer comment:

Without confirmed clinical details, causal relationship between the reported symptoms and levonorgestrel cannot be established in this case.

Case# 8494195 (domestic, ISR#s 8259905 and 8261704): This is a spontaneous report from a 28-year-old female (LMP unknown) who took Plan B One-Step on an unspecified date for emergency contraception. On an unspecified date, she reportedly experienced “cramps in her chest” and thought she was “having a heart attack.” She also recalled having had “a few Monster energy drinks and a few cups of coffee earlier that day.” She went to an emergency room, where unspecified lab work and tests were performed. She was released from the emergency room after a few hours. In addition, she reported having brown vaginal discharge and a heavier period than normal on an unspecified date. This case was not medically confirmed and no additional information is available.

Medical officer comment:

Coding the events as myocardial infarction (MI) based on the verbatim terms reported by the consumer is inappropriate. There is no evidence that she had an MI, as her evaluation in the emergency room only lasted a few hours. Her symptoms of chest discomfort are most likely related to the caffeinated beverage she consumed earlier during the day. Irregularity of her vaginal bleeding is not unexpected after taking levonorgestrel.

Case# 8556679 (domestic, ISR# 8351399): This is a spontaneous report from the boyfriend of a 15-year-old female (LMP April 18, 2012) who took Plan B One-Step on April 28, 2012 for emergency contraception. Following a second episode of unprotected intercourse on April 30, 2012, she took a second dose of Plan B One-Step. She reportedly experienced nausea and vomited blood on May 1, 2012. The report was not medically confirmed and there is no additional information available.

Medical officer comment:

Nausea is a common side effect after taking levonorgestrel for emergency contraception. Under fasting conditions, the elimination half-life of levonorgestrel 1.5 mg tablet is 27.5 (\pm 5.6) hours.² It is conceivable that taking two doses of Plan B One-Step in three days increased her risk for developing nausea and vomiting. The reporter did not indicate that the bleeding (amount not described) necessitated visits to a healthcare professional or a hospital for evaluation. The hematemesis may have been due to retching; there is no indication of a serious underlying medical condition or serious consequences.

² Plan B One-Step prescription label, section 12.3 Pharmacokinetics.

Case# 8527562 (foreign, ISR# 8307587): This is a literature report of a case of congenital anomaly from the Slovak Republic.³ A male fetus of a 27-year-old, primigravid female was diagnosed at 12⁴ weeks gestation with sirenomelia apus. The mother had taken levonorgestrel 1.5 mg 80 hours after intercourse and had been treated for a urinary tract infection with trimethoprim/sulfamethoxazole 960 mg twice daily on days 14-19 after conception. There was no other known exposure to possible teratogens. Family history was non-contributory.

The first trimester ultrasound revealed a living, malformed, singleton fetus (crown rump length 62 mm/12w4d) with apus (one femur, one small tibia, and no feet), intra-abdominal unilocular cystic structure measuring 10.8 x 7.3 mm, and a two-vessel umbilical cord with allantoic cyst measuring 10 mm in diameter. Bladder and kidneys were not visualized. Amniotic fluid volume was normal. Chorionic villi sampling revealed normal male karyotype of the fetus (46, XY). The parents opted for pregnancy termination on an unspecified date following counseling.

Medical officer comment:

Sirenomelia (also termed the mermaid syndrome) is the most extreme example of the caudal regression syndrome and a rare congenital deformity. It involves fusion of the lower extremities and major visceral anomalies; its incidence has been estimated to be approximately 1 in 100,000 births.⁴ To date, fewer than 20 cases of sirenomelia diagnosed in the first trimester have been reported in the literature.³ Pathognomonic features include other severe caudal defects in the spine, absent or malformed kidneys, anal atresia, and absence of external genital organs. The prognosis is fatal; the babies are either stillborn or succumb soon after birth as a result of profound oligohydramnios and associated pulmonary atresia, severe lower genitourinary and lower gastrointestinal abnormalities. The etiology is still unknown, but some reports have suggested an association with monozygotic twinning, maternal diabetes, genetic factors, vascular anomalies, and teratogens exposure (such as cocaine, cadmium, radiation, isotretinoin).^{3,5,6}

The authors of this case report considered exposure to trimethoprim during pregnancy a possible factor in the development of sirenomelia, citing the timing of exposure to this folic acid antagonist. They note that trimethoprim “easily crosses placental barrier and affects the development of the mesodermic axis and caudal blastem” and that the period “between 24 and 36 days in the human embryonic development is most vulnerable for lower extremities defects.” There was no attribution of causal relationship to levonorgestrel. A literature search identified another case report that speculated on a possible trimethoprim-related etiology to caudal regression syndrome.⁶ The report

³ Dosedla E, Kalafusová M, Calda P. Sirenomelia apus after trimethoprim exposure: first-trimester ultrasound diagnosis – a case report. J Clin Ultrasound 2012; March 29 [Epub ahead of print].

⁴ Källén B, Castilla EE, Lancaster PAL, Mutchinick O, Knudsen LB, et al. The cyclops and the mermaid: an epidemiological study of two types of rare malformations. J Med Genet 1992; 29:30-35.

⁵ Horikoshi T, Kikuchi A, Tatematsu M, Matsumoto Y, Hayashi A, et al. Two cases of a fetus with sirenomelia sequence. Congenital Anomalies 2005; 45:93-95.

⁶ Rojansky N, Fasouliotis SJ, Ariel I, Nadjari M. Extreme caudal agenesis. Possible drug-related etiology? J Reprod Med 2002; 47(3):241-5.

concerned a male fetus of a 28-year-old primigravid woman was diagnosed in the second trimester by ultrasound to have extreme hypotrophy of the caudal body pole and complete renal agenesis. Review of maternal history revealed the use of topical 2% minoxidil solution for hair loss for four years prior to and during gestation. Also, the pregnancy was conceived following clomiphene citrate induction and the mother had taken trimethoprim-sulfamethoxazole (two tablets, twice daily for two weeks) and erythromycin (0.5 g four times daily for one week) during the first trimester for treatment of upper respiratory disease. However, given the rarity of caudal regression syndrome and sirenomelia, the authors cautioned that a definitive relationship between maternal exposure to these drugs (single-agent or in combination) and the congenital abnormalities cannot be assumed. Trimethoprim/sulfamethoxazole is labeled pregnancy category C – to be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.⁷

Finally, levonorgestrel is not known to be associated with congenital anomalies. Based on the limited information available, it would be difficult to implicate levonorgestrel in the reported outcome of sirenomelia in this case.

Case# 8544633 (foreign, ISR# 8334073): This is a spontaneous report from a consumer whose age, LMP, and medical history are unknown. She reported taking Levonelle (levonorgestrel 1.5 mg) on an unspecified date following unprotected intercourse. She reportedly became pregnant and subsequently had a miscarriage on an unspecified date. The consumer also stated that this was the second time she had taken Levonelle for emergency contraception and had a pregnancy that ended in miscarriage. There was no medical confirmation for the information provided, and no additional clinical data are available.

Case# 8547535 (foreign, ISR# 8338108): Based on the narrative provided in the report, this case appears to be a duplicative report of case# 8544633 discussed above.

Medical officer comment:

No emergency contraceptive methods are 100% effective; one in eight pregnancies would not have been prevented despite taking levonorgestrel 1.5 mg for emergency contraception.

As for the 1,569 non-expedited reports, all were spontaneously reported by consumers and lacked medical confirmation. Among the 1,569 non-serious cases, a total of 1,423 pertained to initial cases while 146 were follow-up reports already received by Teva in previous PADERS (thus already reviewed by FDA). Of the 1,423 non-expedited cases, a total of 1,106 (78%) reported adverse events that are already labeled. The remaining 317 cases reported non-serious and unlabeled AEs, which were non-specific and lacked any discernable patterns. The most commonly reported adverse events (AEs) in this PADER were menstrual irregularities (881 counts of 2,547 total AE count), pelvic pain (172 counts of 2,547), nausea (156 counts of 2,547), and vomiting (123 counts of 2,547). The nature and frequencies of these events are unchanged relative to the findings from previous PADERS submitted for Plan B One-Step.

⁷ Prescription label for Bactrim™ (sulfamethoxazole and trimethoprim) DS, August 29, 2012 version.

3. CONCLUSIONS AND RECOMMENDATIONS

No new safety issues are identified from this PADER. Continuing routine postmarketing surveillance is recommended.

Table 1. Summary of 15-day reports received by Teva during the quarter of April 1, 2012 to June 30, 2012

AERS Case #	AERS ISR #	Teva Case#	Age	FDA received date	Event date	Source	Outcome	Adverse events (MedDRA PT)
8493795	8259261 8261857	US-TEVA-331374USA	?	April-4-2012 April-5-2012	March-31-2012	Consumer	OT	Hypersensitivity, dysarthria, pain in extremity, tremor, trismus
8494195	8259905 8261704	US-TEVA-331671USA	28	April-4-2012 April-5-2012	April-3-2012	Consumer	OT	Myocardial infarction, chest pain, vaginal discharge, menstruation irregular
8556679	8351399	US-TEVA-335907USA	15	May-10-2012	May-1-2012	Consumer	OT	Haematemesis, nausea
8586662	8396420 8423262 8427715 8503218	GB-TEVA-339222ISR	22	May-30-2012 June-8-2012 June-11-2012 July-11-2012	May-13-2012	Physician	DE, HO	Lemierre syndrome, sepsis, peritonsillar abscess, multi-organ failure, cavernous sinus thrombosis, jugular vein thrombosis, lymphadenopathy, eye discharge
8527562	8307587	CZ-TEVA-334314ISR	0	April-24-2012	Unspecified	Literature Physician	CA	Caudal regression syndrome, foetal exposure during pregnancy
8544633	8334073	GB-TEVA-335424ISR	?	May-3-2012	Unspecified	Consumer	OT	Abortion spontaneous, pregnancy after post-coital contraception, maternal exposure during pregnancy
*8547535	8338108	GB-TEVA-335425ISR	?	May-4-2012	Unspecified	Consumer	OT	Abortion spontaneous, pregnancy after post-coital contraception, maternal exposure during pregnancy

PT: preferred term

OT: other definition for serious outcome designated by the applicant

Blue: foreign cases

*Case 8547535 is a duplicative report of case# 854463

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/s/

CHRISTINA Y CHANG

09/04/2012

LESLEYANNE FURLONG

09/04/2012

CLINICAL REVIEW

Application Type	NDA, Complete Response to the December 7, 2011 Action Letter
Application Number(s)	21-998/S-002
Priority or Standard	Standard
Submit Date(s)	March 9, 2012
Received Date(s)	March 9, 2012
PDUFA Goal Date	September 9, 2012
Division / Office	DNCE / ODE IV
Reviewer Name(s)	Christina Chang
Review Completion Date	May 19, 2012
Established Name	Levonorgestrel
Trade Name	Plan B One-Step
Therapeutic Class	Progestin
Applicant	Teva Women's Health, Inc.
Formulation(s)	Oral tablet
Dosing Regimen	One tablet as soon as possible
Indication(s)	Emergency contraception
Intended Population(s)	Females of reproductive potential, age 15 years and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend an **Approval** action for the applicant's amended request to further expand OTC marketing of Plan B One-Step to adolescents 15 and 16 years of age, pending satisfactory negotiation of labeling.

Plan B One-Step (1.5 mg levonorgestrel tablet) for use as an emergency contraceptive (EC) was approved on July 10, 2009 to allow over-the-counter (OTC) marketing for women aged 17 years and over and prescription marketing for women younger than 17 years of age. In the first submission of this supplemental application (sNDA), the applicant sought to expand OTC marketing of Plan B One-Step to adolescents under age 17 years to make the product available OTC to all women of reproductive potential. While there was consensus within FDA that scientific data provided by the applicant adequately met the regulatory requirements to support eliminating the prescription requirement for all adolescent females of reproductive potential,¹ the sNDA ultimately was not approved because the Secretary of Health and Human Services (HHS) issued an unprecedented directive overruling FDA's decision.² In her December 7, 2011 memorandum documenting her decision not to approve the sNDA, the Secretary specifically cited insufficient data on the youngest adolescents to mitigate her concern that these young adolescents may not possess cognitive and behavioral capabilities to make appropriate decisions about whether to use Plan B One-Step. However, the Secretary did not elaborate in her memorandum on how the cognitive and behavioral immaturity in the youngest adolescents would impact their decisions regarding child-rearing if unintended pregnancies were to occur. The action letter issued by CDER to the applicant did not specify what data would be required to address the Secretary's concern.

1.2 Risk Benefit Assessment

In this resubmission, the applicant modified the OTC marketing proposal to include a lower age limit. If approved, females aged 15 years and over would be able to purchase Plan B One-Step without a prescription. The applicant also proposes to restrict distribution of this product to pharmacies only where an age-verification protocol will be in place. This Complete Response contained no new clinical data; my review of the postmarketing safety data included in this resubmission and my assessment of an updated literature search identified no new issues that would alter the conclusion I reached in the previous review cycle. My opinion regarding this supplemental application thus remains unchanged: the benefit/risk determination remains in favor of OTC availability to ensure timely EC access for all post-menarchal adolescent females seeking to prevent unintended pregnancy.

Although I am sensitive to the consideration that the youngest adolescents may benefit from interaction with healthcare providers to discuss the use of EC, I remain concerned that prohibiting OTC access to Plan B One-Step for adolescents under age 15 years, as proposed, would not mitigate the problem of delayed access to EC in this population should the need for EC arise. I continue to believe that Plan B One-Step should be approved for OTC use without a lower age limit.

Results of the CDC's 2009 national Youth Risk Behavior Survey (YRBS) indicated that among high school students (grades 9 through 12) nationwide, 34.2% were currently sexually active (defined as having had sexual intercourse within three months prior to completing the survey); of these students who were sexually active, 38.9% had not used a condom during their last episode of sexual intercourse.³ Comparative data estimating the proportions of currently sexually active adolescents in the younger age groups are not as readily available, since CDC's Middle School Youth Risk Behavior Survey (YRBS-MS) does not utilize the same questionnaire used in YRBS. However, it would be reasonable to expect lower proportions of sexually active adolescents aged 14 years and younger compared to those 15 years and older. This expectation is supported by data from national surveys reported by Albert et al.⁴ These results indicate lower percentages of adolescents, especially those 12- or 13-years old, engaging in sexual activity compared to those aged 15 years and older, as shown in Table 1 below.

Table 1. Percentage of adolescent females who report no sexual activity in the 18 months preceding the interview, by age

Age (years)	Female	Male	Total number in survey
12	98%	95%	357
13	96%	93%	1719
14	88%	87%	2109

The need of EC for these very young adolescents (12- to 14-year-olds) is real and should by no means be dismissed.

However, I am also mindful that it has been a decade since the original OTC application requesting OTC status for Plan B was submitted to FDA on April 23, 2003. In the interest of enhancing access to adolescents 15- and 16-year-old, I regard the applicant's new proposal an improvement over current labeling. The applicant's proposal in this CR appears to reasonably address the HHS Secretary's concern, which focused on the very youngest adolescents. Therefore, I consider the proposed labeling change for target population acceptable at this time. My decision to recommend approval for the labeling change proposed in this CR recognizes the fact that birth rate among adolescents aged 15 to 17 years of age exceeds that among adolescents 10 to 14 years.⁵ Based on data collected by CDC's National Vital Statistics System, the birth rate for females (all races/ethnicity) 15- to 17-year-olds was 21.7/1,000 females in 2008, compared to 0.6/1,000 females among those 10- to 14-year-olds. Expanding OTC access to adolescents aged 15- and 16-year-old can be an important milestone in the effort to prevent teen pregnancy. Based on the applicant's experience of difficulty in recruiting the very young adolescents in the actual use studies, it is known that these very young adolescents represented a

small proportion of EC-seeking population. While I firmly believe the favorable LCS and AUS results for Plan B One-Step can be extrapolated to these very young adolescents, currently they can access EC through interaction with healthcare providers. I take some comfort in that EC is available to them in the form of prescription Plan B (and its generic products) and ulipristal acetate (Ella). Nevertheless, I recognize that having very similar products (Plan B and Plan B One-Step) with different labeling is less than ideal and I strongly encourage the applicant to consider labeling revision in the near future to remove all age restriction.

In my review of the first submission to this sNDA dated October 5, 2011, I outlined the rationales underlying my recommendation in favor of OTC access to Plan B One-Step for adolescent females. Since the writing of my first review, there have not been any new data to undermine the strength of these rationales. I reiterate the rationales underlying my decision to recommend approval of this sNDA as the following:

1. Unintended teen pregnancy remains a major public health issue in the U.S.

The pregnancy rate among U.S. adolescents remains high compared with other industrialized countries. In 2009, the Center for Disease Control and Prevention estimated that 740,000 pregnancies occurred in adolescents aged ≤ 17 years in 2005.⁶ Of these 740,000 pregnancies reported in 2005, 57% (422,000) resulted in a live birth, 27% (203,000) ended in an induced abortion, and 16% (116,000) ended in a spontaneous fetal loss. A total of 16,000 pregnancies were estimated to have occurred among adolescents under age 15 years; of these, an equal number (approximately 7,000) resulted in live births and induced abortions, while 2,000 ended in spontaneous fetal losses.

Adolescent pregnancies incur enormous societal costs. Short-term and long-term adverse health consequences of teen pregnancy have been documented for both the mother and child.⁷ Adverse economic consequences have also been documented for teen mothers and for their children. Adolescent mothers have lower educational attainment and are more likely to be affected by poverty. The National Campaign estimated in 2006 that teen childbearing costs taxpayers at least \$9.1 billion annually.⁸

Despite the fact that the majority of adolescent pregnancies resulted in live births, evidence shows that a large proportion of these pregnancies were unintended. Findings of an analysis by Finer et al. indicate that 100% of the pregnancies in those younger than 15 had been unintended, compared to 87% of pregnancies in 15- to 17-year-olds (based on 2001 data).⁹ Finer et al. also showed that abortion rate correlated with the “intendedness” of pregnancies. Specifically, 51% of the pregnancies occurring in adolescents younger than 15 years ended in induced abortion, whereas 39% of unintended pregnancies occurring in those aged 15 to 17 years ended in abortion. Preventing unintended pregnancies from occurring can decrease the number of abortions in adolescents.

Therefore, I believe that a public health problem of this magnitude should be addressed with all armamentaria available, including increased access to emergency contraception for those who choose to use it.

2. Emergency contraception has a limited therapeutic window.

The small therapeutic window of levonorgestrel when used as an emergency contraceptive (EC) makes timely access to this product essential. Although the approved labeling for levonorgestrel EC recommends that the product be taken within 72 hours of unprotected intercourse, it is important to note that the EC efficacy is inversely related to elapsed time following unprotected intercourse. Data supporting the Plan B marketing application showed that earlier use of EC increases efficacy. The multi-national study sponsored by the World Health Organization (WHO)¹⁰ found a pregnancy rate of 0.4% if levonorgestrel is taken within 24 hours following unprotected intercourse, compared to pregnancy rates of 1.2% and 2.7% if levonorgestrel is taken in the 25-48 hour and 49-72 hour windows, respectively. Clearly, for women who have had unprotected sex, access to EC within 24 hours of coitus offers the greatest likelihood to avoid unintended pregnancy. OTC, rather than Rx availability is more likely to allow earlier use of EC in this limited window.

That having been said, the current reality is that when an adolescent finds herself in need of EC, she is likely to face significant logistical and financial barriers in obtaining EC. Specifically, she would need to identify a healthcare provider, secure an appointment with this provider, obtain the prescription for EC, and purchase the product from a pharmacy that has it in stock, all within 72 hours. Although the practice guideline issued by the American College of Obstetricians and Gynecologists does not require a clinical examination prior to provision of EC,¹¹ the reality is that few providers would prescribe EC for an adolescent whom they have not previously seen in the office as a patient. In the opinion of this medical officer, the potential risk of unintended pregnancy or subsequent pregnancy termination resulting from delayed access to EC carries a far greater clinical significance for the adolescents than their possible misuse of a single dose of levonorgestrel EC.

3. There is no unique safety concern for levonorgestrel emergency contraception in adolescents.

Levonorgestrel as an active ingredient has a decades-long safety record. Since the prescription (Rx) approval of Plan B in 1999, a favorable safety profile of levonorgestrel used as EC has also been shown. The mechanism of action of levonorgestrel EC in post-menarcheal females is the same, regardless of age. The side effect profile of levonorgestrel EC is not distinguishable based on age of the user alone. Indeed, my review has not identified unique safety signals for levonorgestrel EC specifically in adolescents (compared with adults).

After reviewing postmarketing safety information of levonorgestrel EC products (time period: January 1, 2002 through December 31, 2010), the Pediatric Advisory Committee (PAC), which met on January 30, 2012, also reached the conclusion that there were no age-related differences in the safety profile of levonorgestrel EC products. The PAC review was mandated by the Best Pharmaceuticals in Children Act (BPCA) and the

Pediatric Research Equity Act (PREA). The statutes require an examination of pediatric safety data by the PAC, which was triggered by the 2009 approval of Plan B One-Step. The PAC was reassured with the safety information regarding levonorgestrel EC products and concluded that levonorgestrel EC is safe in women of all ages. The PAC thus recommended that FDA continue routine postmarketing safety monitoring for Plan B One-Step. The vote tally was overwhelmingly in support of routine monitoring – 21 voted yes, no one voted no, and one member abstained. Furthermore, some members of the PAC expressed support for the same recommendations made by the 2003 joint Advisory Committee for OTC availability without age restriction. These members urged the FDA not to discriminate against adolescents by limiting their access to the product. The reader is referred to additional discussion on the PAC’s deliberation under section 9.3, Advisory Committee Meeting.

4. Results of consumer studies submitted in the original sNDA satisfactorily demonstrate that adolescents can understand the product label and use Plan B One-Step safely and appropriately.

As discussed under section 5.3.1 of my October 5, 2011 review, results of the label comprehension study (LCS, DR-LEV-301) have demonstrated successful comprehension of key elements of the label by adolescents. Also, as discussed in detail under section 5.3.2.4 of my 2011 review (under medical officer comment), results of the actual use study (AUS, DR-LEV-302), now published,¹² have demonstrated that 99% of the adolescent subjects were able to correctly self-select to take Plan B One-Step, and that 92.3% of subjects were able to use the product correctly. Furthermore, when compared to adult subjects who participated in the actual use study for Plan B, these adolescent subjects performed favorably with respect to correct product usage. With respect to label comprehension study data, results of DR-LEV-301 also compared favorably with the label comprehension study conducted to support the Plan B OTC switch application. For one communication objective in the Plan B One-Step label in particular, the adolescents in DR-LEV-301 demonstrated superior understanding in comparison with adult subjects. While 92.2% of DR-LEV-301 subjects understood that Plan B One-Step should not be used for regular contraception, 67% of the mostly adult subjects in the Plan B label comprehension study understood that Plan B should not be used for regular contraception. Thus, the adolescent LCS and AUS data submitted by the applicant have satisfactorily mitigated the concerns raised by Dr. Galson previously. OTC marketing of Plan B One-Step should be available to the adolescent population.

5. Availability of EC has not been shown to adversely affect the contraceptive behavior. To date, clinical trials have been consistent in demonstrating a lack of association between advance provision of EC and adverse reproductive health outcomes subsequently (with follow-up up to 12 months).¹³⁻¹⁸ Specifically, advance provision of EC has not been shown to increase the incidence of sexually transmitted diseases, decrease condom use, encourage adoption of less reliable contraceptive methods, or otherwise negatively affect sexual and reproductive behavior. While I am sensitive to the concerns for the potential of adolescents engaging in more risky behavior, available

scientific data to date have consistently allayed such concerns. Consequently, I do not believe these concerns should eclipse the efforts to ensure that all adolescents have enhanced access to EC when and if they choose to use it. In addition, considering the side effects of repeated use (for example, irregular bleeding, nausea, and vomiting), the package configuration (each package contains only a single tablet), and cost (one package of Plan B One-Step currently costs as much or more than a one-month supply of oral contraceptive pills), I believe it is unlikely for sexually active adolescents to resort to EC as their long-term, routine contraceptive.

6. Having the same labeling for contraceptive products for all females of reproductive age is consistent with the Agency's past regulatory paradigm

It should be noted that FDA's findings for efficacy and safety of Plan B One-Step did not specify a lower-bound age limit. Furthermore, not stating a lower age limit in the target population is consistent with FDA's past decisions on contraceptive drug products (hormonal contraceptives and spermicides) and barrier device methods (condoms and diaphragms). These decisions were based on the understanding that reproductive physiology, rather than chronological age, determines the need for contraception. I continue to believe that no lower age limit is necessary because Plan B One-Step is safe and effective for all females of reproductive age, and the age at which reproductive ability occurs is variable.

7. OTC switch for levonorgestrel EC without age restriction was overwhelmingly endorsed by the 2003 joint session of the Nonprescription Drug Advisory Committee (NDAC) and the Advisory Committee for Reproductive Health Drugs (ACRHD).

Of the 27 members who cast votes on whether marketing status for Plan B should be switched to OTC, 23 voted yes while four voted no. Members of the joint Advisory Committee reached their decision after considering efficacy and safety data of Plan B, as well as results from the label comprehension study and actual use study provided in NDA 21-045/S-011. Having weighed the benefit of EC against the risk of misuse, the majority of the panel supported the switch **without age restriction**. I concur with the panel's recommendation. The reader is referred to detailed discussion and summary of the Committee's deliberation presented in my 2011 review (under section 9.3, Advisory Committee Meeting).

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None; as per the law, postmarketing Risk Evaluation and Mitigation Strategies are not applicable to OTC products. Further, the CARE program, implemented in 2006 to monitor adherence to the dual labeling for Plan B and voluntarily extended by the applicant for Plan B One-Step in 2009, would become obsolete if this supplemental application becomes approved.

1.4 Recommendations for Postmarket Requirements and Commitments

None recommended beyond routine postmarketing surveillance.

2 Introduction and Regulatory Background

2.1 Product Information

OTC marketing of Plan B One-Step (1.5 mg levonorgestrel tablet) for use as an emergency contraceptive was approved for women aged 17 years and over on July 10, 2009. Efficacy and safety of Plan B One-Step as an emergency contraceptive is already well-established. In this amended supplemental application, the applicant proposes to expand OTC marketing to adolescents aged 15 and 16 years of age.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 2. Approved treatments for emergency contraception

Propriety (pharmacological) name	Formulation	Approval mechanism	Marketing status
Plan B and its generics (levonorgestrel 0.75 mg)	Tablet	NDA 21-045, ANDAs 78-665/90-740	OTC for 17 and older; Rx for 16 and under
Ella (ulipristal acetate 30 mg)	Tablet	NDA 22-474	Rx
Preven Emergency Contraception Kit (ethinyl estradiol 0.05 mg/levonorgestrel 0.25 mg)	Tablet	NDA 20-946	Rx (no longer marketed for business reasons)

Of note, an old EC regimen utilizes combination oral contraceptive pills taken as a two-dose, 12-hour regimen; each dose contains 100 mg ethinyl estradiol and 0.5 mg levonorgestrel (the Yuzpe regimen).¹¹

2.3 Availability of Proposed Active Ingredient in the United States

The active moiety in Plan B One-Step, levonorgestrel, is a second-generation progestin with an established record of safe use; it has been used in prescription (Rx) contraceptive products for over four decades. Levonorgestrel is the progestin component in combination oral contraceptives with daily dosages ranging from 0.05 mg to 0.15 mg. In contrast with the European market, where progestin-only oral contraceptives containing levonorgestrel at a daily dose of 0.03 mg have been marketed for more than three decades, there are no approved oral contraceptive formulations containing single-ingredient levonorgestrel in the U.S.

Levonorgestrel is also found as a single ingredient in FDA-approved contraceptive implants (Norplant, Norplant II) and an intrauterine device (Mirena). Finally, levonorgestrel is also FDA-approved in a two-dose regimen (0.75 mg per dose, for the same cumulative dose of 1.5 mg) for

emergency contraception as Plan B and three generic products. Table 3 presents approved products other than Plan B One-Step containing levonorgestrel.

Table 3. Available therapies other than Plan B One-Step which contain levonorgestrel

Therapeutic class	Examples	Marketing status
Combination oral contraceptives	Enpresse-28, Seasonale	Available in and outside U.S.
Progestin-only oral contraceptives	Norgeston, Microval	Not available in U.S.
Implants	Norplant, Norplant II	No longer marketed in U.S.
Intrauterine device	Mirena	Available in and outside U.S.
Emergency contraception	Plan B and its generic versions	Available in and outside U.S.

2.4 Important Safety Issues With Consideration to Related Drugs

There is a well-established favorable safety profile for progestin-only drugs. Levonorgestrel, the active moiety in Plan B One-Step, has a wide margin of safety. In clinical trials, the most commonly reported adverse events were menstrual changes, nausea, abdominal pain, fatigue, headache, and dizziness. Considering that the use of Plan B One-Step is limited to a single dose, significant safety issues are not expected.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Plan B One-Step and the closely related product, Plan B, have had a lengthy and intertwined history, necessitating numerous interactions between the Agency and the applicant*. A detailed, chronological account of the regulatory history pertinent to Plan B One-Step through February 7, 2011, is summarized in my review (dated October 5, 2011) of this supplemental application's first submission.

During the Agency's review of data submitted to support over-the-counter status for Plan B (NDA 21-045, Supplement-011, 0.75 mg levonorgestrel tablet, two doses taken 12 hours apart), then Acting CDER Director Dr. Steven Galson concluded that an insufficient number of adolescents was included in the label comprehension and actual use studies conducted to support non-prescription marketing of Plan B without age restriction.¹⁹ Specifically, Dr. Galson noted that only 76 of 656 eligible subjects in the label comprehension study were \leq 16 years old, and only 29 of 585 eligible subjects who were dispensed Plan B in the actual use study were \leq 16 years old (20 of the 29 were 16 year-olds). As a result, Dr. Galson rejected the recommendations made by a Joint Advisory Committee and the Agency's review staff to approve the OTC switch of Plan B for all females of reproductive potential. In 2006, the OTC switch application was ultimately approved for women age 18 and older but not approved for adolescents under 18 years of age. Plan B remained a prescription drug for adolescents under 18 years of age. Thus, age

* There have been a number of applicants for Plan B and Plan B One-Step due to acquisitions: Women's Capital Corporation, Barr Research Inc, Duramed Pharmaceuticals Inc, and Teva Women's Health Inc. For ease of reference, all are referred to as "the applicant" in this review.

became the sole factor in determining the marketing status of Plan B, with OTC marketing available to women age 18 and older. The unusual nature of the review process for the Plan B switch application and the resultant decision have been documented in the Government Accountability Office's November, 2005 report to Congress.²⁰ When Plan B One-Step was approved in July 2009, FDA's scientific review concluded, in response to a federal court mandate to reexamine adolescent data, that both Plan B and Plan B One-Step should be labeled as OTC products for women 17 years of age and older.

In order to address the deficiency raised by Dr. Galson, the applicant conducted a label comprehension study (DR-LEV-301) and an actual use study (DR-LEV-302) in adolescents 17 years of age and younger using Plan B One-Step, which has a simpler dosing regimen than Plan B. On February 7, 2011, the applicant submitted a supplemental application to FDA, requesting to expand OTC marketing for Plan B One-Step from being available to women 17 years of age and older to all females of reproductive potential. FDA's review of the February 2011 sNDA concluded that data from DR-LEV-301 and DR-LEV-302 provided sufficient support to demonstrate that Plan B One-Step should be approved for OTC use to all females of reproductive potential without a lower age limit. This decision was unanimous throughout the Center for Drug Evaluation and Research (CDER) review chain, and was supported by Dr. Margaret Hamburg, the FDA Commissioner, who agreed with CDER that "there is adequate and reasonable, well-supported, and science-based evidence that Plan B One-Step is safe and effective and should be approved for nonprescription use for all females of child-bearing potential."¹

However, on December 7, 2011, the Secretary of Health and Human Services (HHS), Ms. Kathleen Sebelius, overrode the FDA's decision and ordered FDA not to approve the sNDA, as proposed. In her memorandum dated December 7, Secretary Sebelius stated her determination that data submitted in the sNDA were insufficient to support elimination of prescription dispensing requirements for adolescents who wish to purchase Plan B One-Step.² Citing the "cognitive and behavioral differences between older adolescent girls and the youngest girls of reproductive age," as well as the lack of data for the youngest adolescents from DR-LEV-301 and DR-LEV-302, the Secretary directed CDER to issue a Complete Response letter to the applicant. In rejecting the sNDA's proposal for OTC access to Plan B One-Step without age restriction, Secretary Sebelius' rationale for rejecting the sNDA appears to be essentially indistinguishable from that previously stated by Dr. Galson, namely that it would be inappropriate to extrapolate results of the label comprehension and use study data from older adolescents to the youngest adolescents.

On March 9, 2012, the applicant submitted a Complete Response to FDA in response to the December 7, 2011 action letter. This second submission revised the OTC labeling to reflect a new age restriction, proposing OTC access to adults and adolescents 15 years of age and older. The request is supplemented by a proposal for restricted distribution to pharmacies implementing an age-verification protocol.

2.6 Other Relevant Background Information

Following the unprecedented action by HHS Secretary Sebelius to overrule FDA's decision on December 7, 2011, three medical organizations with expertise in adolescent care – the American Academy of Pediatrics (AAP), the American College of Obstetricians and Gynecologists (ACOG), and the Society for Adolescent Health and Medicine (SAHM) – issued a joint statement expressing disappointment with the Secretary's decision.²¹ Taking issue with the Secretary's decision to deny approval of the sNDA, Dr. Robert Block, the president of AAP, stated that continuing "restricting access to this safe and effective product is medically inexplicable." Dr. Block gave this perspective: while "the AAP recommends that adolescents postpone sexual activity until they are fully ready for the emotional, physical, and financial consequences of sex," however, "as physicians who care for our nation's children, it is our responsibility to protect the health of our teenage patients, and an unintended pregnancy can have significant implications for adolescents' physical and emotional health." I concur with Dr. Block's statement.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This resubmission contains no new clinical trial data. The applicant makes reference to three separate Periodic Adverse Drug Event Reports (PADERS) submitted to FDA after the original sNDA had been accepted for filing. Although each PADER satisfies the regulatory requirement in summarizing postmarketing safety data obtained by the applicant for the three months prior, the quality of the resubmission would have been strengthened if the applicant had provided an overarching safety analysis spanning the nine-month interval.

In addition, a fourth PADER was submitted on April 30, 2012 to the original NDA. For the sake of completeness, this review encompasses information from the fourth PADER, even though the applicant has not amended the CR to include this latest PADER.

3.2 Compliance with Good Clinical Practices

Not applicable; no new clinical studies were conducted for this resubmission.

3.3 Financial Disclosures

Not applicable, since no new clinical studies have been conducted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

The study product, Plan B One-Step, is already an approved product subject to this NDA. The study drug is supplied to Teva Women's Health, Inc. by Gedeon Richter Ltd. (Budapest, Hungary), the same manufacturer for approved Plan B and Plan B One-Step products. Therefore, there are no issues pertinent to chemistry, clinical microbiology, pharmacology/toxicology, or clinical pharmacology.

5 Sources of Clinical Data

The primary clinical data to support this sNDA consists of the open-label, non-comparative actual use study, DR-LEV-302. The other consumer study submitted to support this application, DR-LEV-301, is a label comprehension study where no subjects were administered any study product. Both of these studies were reviewed by FDA in the first review cycle.

There are no new efficacy data submitted in this supplemental application. Updated information provided by the applicant is comprised of postmarketing safety data from a nine-month period as a safety update. The applicant makes references to three individual Periodic Adverse Drug Events Reports (PADERs) submitted to FDA on July 31, 2011, October 31, 2011, and January 31, 2012. FDA also received another PADER on April 30, 2012. These are discussed under section 8, Postmarket Experience.

5.1 Tables of Studies/Clinical Trials

This resubmission does not include any data from new clinical trials.

5.2 Review Strategy

Given that there are no new clinical data, the scope of this review is limited to the three Periodic Adverse Drug Event Reports (PADERs) referenced by the applicant, as well as an interval literature search. Each PADER is reviewed separately, focusing on cases considered by the applicant to have had a serious outcome. All available information provided by each case report is examined in detail. The reader is referred to individual case narratives and summary tables presented under section 8, Postmarket Experience. Furthermore, an integrated safety analysis on all four PADERs can be found in Safety Summary under section 7, Review of Safety.

Additionally, my review of labeling compared the following three versions of the label:

- Plan B One-Step label approved on July 10, 2009;
- Proposed Plan B One-Step labeling language submitted on December 7, 2011. This is the version that FDA would have approved had the HHS Secretary not overruled the action intended by FDA;
- Proposed Plan B One-Step label submitted in this Complete Response on March 9, 2012.

My labeling comments are included under section 9.2, Labeling Recommendations.

5.3 Discussion of Individual Studies/Clinical Trials

The reader is referred to my October 5, 2011 review for the original submission to this supplemental application. In the first submission, the application provided data generated from DR-LEV-301 and DR-LEV-302 to support the removal of age restriction at the point of purchase for OTC use in order to address FDA's (Dr. Galson's) 2006 request for data to demonstrate that Plan B can be used appropriately by adolescents.

6 Review of Efficacy

The effectiveness of Plan B One-Step as emergency contraception has been already established for women of all reproductive ages. For additional details on efficacy for Plan B One-Step, the reader is referred to the clinical review by Dr. Daniel Davis for NDA 21-998, dated November 22, 2006.

7 Review of Safety

Safety Summary

Used as an emergency contraception, levonorgestrel has a wide margin of safety as demonstrated by the substantial postmarketing profile since the 1999 Rx approval. Subsequent to the OTC switch of Plan B in 2006, the safety of levonorgestrel used in an OTC setting adds further reassurance. The approval of Plan B One-Step in 2009 took into consideration the

The safety data assessed in the previous review cycle of this sNDA included:

- Safety information included in DR-LEV-302
- Postmarketing safety data from the Teva, from commercial launch of Plan B One-Step on July 10, 2009 to November 30, 2010
- Information from FDA's Adverse Events Reporting System (AERS) for Plan B, Plan B One-Step, and other levonorgestrel EC products from July 10, 2009 to September 30, 2010
- Information from the World Health Organization's (WHO) International Drug Monitoring Program for levonorgestrel EC products from July 10, 2009 to February 15, 2011

The safety findings from DR-LEV-302 are consistent with known profile of levonorgestrel. There were no unexpected serious adverse events and the results of DR-LEV-302 are sufficient to demonstrate that adolescents can appropriately and safely use Plan B One-Step. Analyses performed on data collected in applicant's postmarketing surveillance system as well as AERS and WHO revealed no new safety signals.

The applicant provided updated safety information in this resubmission, by referencing three postmarketing safety reports previously submitted to the FDA but not included in the submission for the original efficacy supplement. These reports covered the period from April 1, 2011 through December 31, 2011. Another PADER, submitted on April 30, 2012, covered the time period from January 1, 2012 through March 31, 2012. Detailed findings from these reports are discussed under Section 8, Postmarketing Experience, of this review.

These four PADERs, which covered a 12-month interval, contained a total of 5,958 cases reporting at least one adverse event involving Plan B One-Step, or its foreign equivalent. As expected, menstrual irregularity (a labeled event) is the most commonly reported adverse event. The other commonly reported events – nausea, pelvic pain, vomiting – are also already included in the current Plan B One-Step label. With the exception of four foreign cases, all among the 5,958 cases were of the voluntary and spontaneous nature, with consumers as the direct sources for reporting. All the U.S. reports originated from consumers spontaneously. These consumer-generated reports offer no convincing indication for any new safety signals, particularly since the verbatim terms were sometimes miscoded by the applicant (for example, blood clots per vaginal coded as “thrombosis”).

Among the 5,958 cases, 41 (0.7%) were classified by the applicant as having serious outcomes. While no deaths were reported, the 41 serious cases included two hospitalizations and two congenital anomalies. The reported hospitalizations were extracted from case reports in literature and were substantiated by clinical details.^{22, 23} The reported cases of congenital anomalies identified in two term infants concerned a infant born with cleft palate and another born with a nevus; the causal relationship with prenatal exposure to Plan B One-Step in these cases is doubtful. More than half of the remaining 37 cases (22 cases) pertained to pregnancy related events such as spontaneous abortion. It is important to note that a certain number of pregnancies (and thus pregnancy-related events) may be expected, as Plan B One-Step would not prevent all pregnancies even if taken correctly by all consumers. The other cases unrelated to pregnancy included hematemesis (3), loss of consciousness (2), blindness (1), Henoch-Schönlein purpura (1), infertility (1), and migraine (1). However, the validity of any of these cases could not be established due to the very scant information provided by in the case narratives.

Overall, these four PADERs present a benign safety profile of Plan B One-Step that is consistent with the current label. Nevertheless, given the serious nature of these events, the two literature reports of hospitalizations – one for deep vein thrombosis (DVT) the other for cerebrovascular accident (CVA) – warrant some discussion. Both cases originated in Spain.

The DVT case occurred in a 22-year-old woman.²² It is noted that she had a history of “epistaxis associated with paracetamol [acetaminophen]” (no other details were provided) and as an art student, was required to “spend several hours each day with her arms in forced positions for sculptures and painting.” Three days after taking levonorgestrel 1.5 mg for emergency contraception, she presented with pain in her right arm of about 24 hours in duration. Physical examination was remarkable for edema and pain on compression of her brachial musculature. A venous Doppler ultrasound of her right arm revealed occlusive thrombosis involving the region

from her humerus to axilla and the juncture of her basilica and cephalic veins. Findings were subsequently confirmed by magnetic resonance venography (MRV). Along with posture-related measures, compression bandage, and physical exercise, she received anticoagulation for 6 months, first with enoxaparin sodium, then with acenocoumarol. Follow-up MRV showed full restoration of permeability in the affected region. The authors attributed the DVT event to have been triggered by the administration of levonorgestrel and the postural stresses brought about by her professional activity.

Nevertheless, it should be noted that, in light of the unusual presentation of upper extremity DVT in this case, the authors' attribution to both levonorgestrel and the patient's postural stresses as causative etiologies is premature. Additional work-up for both hereditary thrombophilia (e.g., genetic polymorphisms, see discussion for the CVA case) and acquired hypercoagulability (e.g., malignancies) should be conducted prior to determining the causality in this case.

The CVA case concerned another woman, who was 23-year-old at the time of the event. No concomitant medications were reported. Her medical history is significant for migraine without aura, and her obstetrical history was notable for one live birth at term and seven miscarriages in both first and second trimesters. There was a positive family history of stroke; her mother at age 45 had a stroke (undetermined etiology). The morning after taking a levonorgestrel 1.5 mg tablet, the patient noted reduced strength and sensitivity in the right side of her body. She presented to the emergency room 36 hours after symptom onset. Neurological examination revealed mild aphasia, diplopia compatible with pseudoparesia of the 4th right cranial nerve, right hemifacial hypoesthesia and right hemiparesis. Cerebral CT and MRI showed cerebral infarction in the left anterior thalamus. A trans-esophageal echocardiogram was negative. Her lipid profile, serology, immunologic, chemistry, and hematologic levels were normal. Hypercoagulability work-up, including anti-phospholipid antibodies, G1691 A factor V Leiden mutation, G20210A prothrombin gene mutation, and protein C/S deficiencies, was negative. Her recovery progressed favorably; three months after the stroke, the only residual was reduced sensation on the right side of the face (NIH stroke scale 1, modified Rankin scale 1, indicating no significant disability).

In my view, it is unlikely that a single-dose of levonorgestrel EC contributed independently to the DVT and stroke experienced by these women. In fact, according to their histories, both women may have had other thrombogenic risk factors that also contributed to their conditions. Specifically, the DVT patient engaged in long periods of decreased arm mobility as required by her professional activity, and the stroke patient likely had other thrombogenic propensities not identified in the work-up, as suggested by her family history and her own poor obstetrical history of recurrent pregnancy losses. In addition, while the thrombophilia work-up conducted in the stroke case may be detailed, it may still not be exhaustive. It appeared that she was not tested for the presence of the homozygosity for polymorphism of C677T (methylenetetrahydrofolate reductase [MTHFR]), another commonly evaluated genetic mutations that have been linked to hypercoagulability.

This stroke case appears to be the first report of stroke associated with progestin-only EC preparation in literature. In the discussion, the authors reporting the stroke case alluded to other literature reports of cerebrovascular accidents temporally associated with the use of EC products; however, patients described in other case reports of stroke all had used EC products containing estrogen in addition to levonorgestrel (the Yuzpe regimen).²⁴⁻²⁶ Potential association between the EC and development of cerebrovascular accident would thus be more likely with the estrogen component of the EC regimen.

While the risks for venous thromboembolic events associated with combination oral contraceptives have long been recognized, the potential for thrombotic events incurred by single-ingredient progestin-only pills is not as clear. It also appears that different progestin preparations may have different properties. For example, among combination oral contraceptive pills, those containing third-generation progestins such as drospirenone have been suggested to confer a greater risk than those containing second-generation progestins such as levonorgestrel.²⁷⁻²⁹ In light of new information on the potential for differential risks imparted by different progestin products, FDA recently revised the label for drospirenone-containing oral contraceptives to include thromboembolic disorders in the **Warnings and Precautions** section.³⁰ Such warnings were not added to levonorgestrel-containing combination OCs. The new OC labeling language thus implicitly recommends levonorgestrel-containing combination OCs for women who have known risk factors for thromboembolic disorders or other vascular problems.

Furthermore, data from the epidemiologic investigations that implicated drospirenone-containing combination OCs also suggest that progestin-only pills are not associated with any increased risk of venous thromboembolism.²⁹ I am not aware of any data to date suggesting that levonorgestrel EC products, when taken in a single dose (as opposed to progestin-only OCs taken daily), may elevate risks for thromboembolism.

Finally, it must be emphasized that any potential increment in thromboembolic risk would still be substantially less than with pregnancy and puerperium. Thus, regarding thromboembolic events, any theoretical, potential risks associated with single-dose levonorgestrel EC must be weighed against a hypercoagulable state of pregnancy that is inevitable.

In summary, considering the extent of world-wide use for progestin-only ECs, I do not believe that single case reports (one DVT with insufficient work-up and one stroke likely due to a hereditary proclivity) rise to the level of warranting labeled warnings at this time. The weight of the evidence currently does not support including warning statements regarding thromboembolism for levonorgestrel ECs. I have arrived at this conclusion based on my assessment of the following:

1. Controlled clinical trial data for levonorgestrel EC (Plan B and Plan B One-Step) did not show a signal for DVT or stroke.^{31,32} The safety database in the pivotal trial for Plan B included 977 women enrolled in the levonorgestrel group, while the Plan B One-Step safety database included 2,756 women, who took either the single-dose 1.5 mg levonorgestrel or the two-dose 0.75 levonorgestrel product.

2. Controlled clinical trial data for Norplant and Norplant II (levonorgestrel-containing subdermal implants) did not suggest a signal for either DVT or stroke. The safety databases included 1,060 women who used Norplant (NDA 19-897, approved on December 10, 1990) and 1,243 women who used Norplant II (NDA 20-544, approved on November 1, 1996).³³ In addition, in an efficacy supplement proposing labeling change for Norplant II from three years of use to five years, the applicant provided additional efficacy trials and expanded the safety database for Norplant II. This supplement included safety data from 5,380 women-years of safety data in the pivotal trials; no thrombosis, stroke, or cardiovascular disease were detected.³⁴
3. Controlled clinical trial data for Mirena, the levonorgestrel-containing intrauterine device (NDA 21-225, approved on December 6, 2000) demonstrated a safety profile consistent with those of other levonorgestrel-containing products. Safety data for Mirena included 5345 women-years of exposure; no DVT, pulmonary embolism, or stroke were observed.³⁵
4. The World Health Organization (WHO) supports the use of levonorgestrel EC in women with history of severe cardiovascular complications.³⁶ WHO lists a history of *ischemic heart disease, cerebrovascular attack, or other thromboembolic conditions* as conditions “where the advantages of using the method generally outweigh the theoretical or proven risks.”
5. U.S. postmarketing data for levonorgestrel EC have not suggested DVT or stroke as safety signals. I searched the AERS database for postmarketing reports identifying “deep vein thrombosis” or “cerebrovascular accident” involving Plan B and Plan B One-Step. The time period covered by this search spans the entire life cycles of Plan B and Plan B One-Step up to the writing of this review (July 18, 1999, the date of the original Rx approval for Plan B, to April 20, 2012). It is reassuring that no case reports were identified by this search.

7.2 Adequacy of Safety Assessments

As stated in my October 5, 2011 review, it is my opinion that the extent of safety information accumulated for levonorgestrel is adequate to support OTC use of Plan B One-Step in all females of reproductive potential.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The principal deficiency cited by Dr. Galson for the actual use study conducted to support Plan B OTC marketing (NDA 21-045) was the small number of adolescents enrolled in the study. Specifically, only 29 adolescents aged 16 years and under were assessed. Of these 29, 20

subjects were 16-year-olds, and there were no data pertaining to adolescents younger than 13-years of age.

In order to address the deficiency outlined by Dr. Galson, the applicant undertook DR-LEV-301 and DR-LEV-302 to assess whether adolescents can understand and appropriately use Plan B One-Step. Despite expanding study enrollment to five geographically diverse sites, only three subjects aged 13 years were enrolled in DR-LEV-302 over a two-year study period. Rationales presented by the applicant to explain the small number of very young adolescents enrolled include the following:

- The average American female does not reach menarche until age 12.³⁷ Premenarchal girls are not at risk for pregnancy and therefore have no reason to use Plan B One-Step.
- The vast majorities of females 11 to 14 years old are not sexually active and therefore are not at risk for pregnancy and have no reason to use Plan B One-Step.^{4, 38-40}
- The pregnancy rate in females 11 to 14 years old is low.⁴¹
- Even in settings where there is pharmacy access to Plan B for people of all ages, the proportion of all Plan B One-Step consumers who are young teens is minimal.
- The likelihood of females 11 to 13 years old presenting to one of the actual use study sites across the country requesting emergency contraception within 72 hours after unprotected intercourse is expected to approach zero.
- It is not appropriate or consistent with the nature or design of this actual use trial to advertise for subjects. Enrollment is therefore dependent on the number of teenagers who spontaneously present to the investigative sites requesting emergency contraception for use in the subsequent three days. The infrequency of this occurrence does not support a minimum enrollment requirement for teens 13 years old and younger.

To put this issue in perspective, the numbers of subjects by age in the respective label comprehension and actual use studies conducted to support OTC switches for Plan B and Plan B One-Step are presented in Table 4 and Table 5 below:

Table 4. Number of subjects by age in label comprehension studies for Plan B and Plan B One-Step

Age	Plan B	Plan B One-Step
≥17	580	55 (all are 17)
16	28	57
15	18	59
14	13	54
13	9	56
12	8	54
Total	656	335

Table 5. Number of subjects by age in actual use studies for Plan B and Plan B One-Step

Age	Plan B	Plan B One-Step
17-44	556	65 (all are 17)
16	20	140
15	7	100
14	2	35
13	0	3
Total	585	343

Data from national surveys indicate that a great majority of adolescents aged 14 and under are not sexually active and have no reason to need EC.⁴ Moreover, the number of adolescents in this age group who 1) are sexually active, 2) request EC, and 3) would be willing to enroll in an actual use study is expected to be exceedingly small as to make such a study not feasible and preclude any meaningful interpretation of study results.

The applicant's rationales are consistent with my experience as an obstetrician and gynecologist; I have considered the rationales and found them to be of merit and thus can be used to justify extrapolation of comprehension and use data from older adolescents to those under age 13 years. The review team determined that the applicant made a reasonable and exhaustive effort to recruit these young adolescents during the conduct of DR-LEV-302.

Nevertheless, in her memo, Secretary Sebelius specifically highlighted the lack of data on "the youngest girls of reproductive age" in rejecting the original supplemental application.² The lead investigator of DR-LEV-302, Dr. Tina Raine-Bennett, has since argued that "it is unreasonable and virtually impossible to study the use of emergency contraception in 11- and 12-year-olds, because only a small fraction of them will have had sex by that age."⁴²

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The reader is referred to my October 5, 2011 review for a discussion on the data from the National Poison Data System (NPDS) maintained by the American Association of Poison Control Centers (AAPCC) and from the Drug Abuse Warning Network (DAWN) database. Following my review of these data, I concluded that Plan B One-Step is unlikely to be a candidate for drug abuse or misuse.

8 Postmarket Experience

In a joint safety review finalized on June 27, 2011, reviewers in the Office of Surveillance and Epidemiology (OSE) and the Division of Reproductive and Urology Products (DRUP) summarized the postmarketing experience for Plan B One-Step from commercial product launch in 2009 to January 31, 2011.⁴³ The review identified no safety concerns that required further assessment. Their findings were presented to the Pediatric Advisory Committee, which met on January 30, 2012 to discuss the pediatric postmarketing safety data for Plan B One-Step. The committee members concurred unanimously that the safety data were reassuring.

In the current submission, the applicant referenced three postmarketing periodic adverse drug event reports (PADER) that had been submitted to FDA. These reports had not been included in the safety update during the previous review cycle. The time periods covered by these three reports totaled nine months; they are discussed below.

PADER 1: covering the period from April 1, 2011 to June 30, 2011

This safety report summarized 1,606 new individual cases received by the applicant. No new safety concerns are raised by these reports.

Of these 1,606 cases, 12 cases were considered by the applicant to have been associated with serious outcomes; nine of these 12 originated from the U.S and three were from foreign sources. All but one (a foreign report) were consumer-generated and not medically confirmed. Excluded from discussion was one U.S. case (Teva case # 283914USA, ISR#s 7527761 and 7542035) pertaining to a seven-week old male infant whose mother took Plan B One-Step for emergency contraception. The infant was treated for five days in the neonatal intensive care following delivery due to meconium aspiration, an event most likely unrelated to Plan B One-Step. The remaining eight domestic cases and three foreign cases classified by the applicant as having serious outcomes are summarized in Table 6. A brief narrative of each case appears below. Each case is listed under a separate case number as recorded in FDA's Adverse Event Reporting System (AERS). The ISR numbers, on the other hand, refer to distinct reports sent to AERS. A particular case may have more than one report.

Case # 7894914 (ISR# 7408410): This is a 26-year-old female with a last menstrual period (LMP) beginning on June 23, 2010. She had unprotected intercourse on July 4, 2010 and took Plan B One-Step on July 5, 2010. A home urine pregnancy test was done on July 18, 2010; the result was negative. She reported subsequent cramping and vaginal bleeding, which culminated in her receiving care in the emergency room for miscarriage on [REDACTED] (b) (6)

Medical officer comment:

Levonorgestrel EC is not 100% effective in preventing pregnancy. Miscarriage is a common complication of pregnancy, with the risk of early pregnancy losses approaching 30%.⁴⁴ Further, miscarriage has not been linked to the use of progestins. This case and other reported miscarriages are related to pregnancy itself, rather than to Plan B One-Step specifically.

Case# 7930290 (ISR#s 7458205, 7470195, and 7531092): This is a 23-year-old female whose LMP started on March 8, 2011. She had unprotected intercourse on March 26, 2011 and took Plan B One-Step on March 26, 2011. She reported breast pain and back pain on March 28, 2011. A home urine pregnancy test done on April 9, 2011 was negative, as was a second test done on April 12, 2011. She experienced vaginal bleeding and cramping from April 13 to May 1, 2011 and sought treatment at the emergency room on [REDACTED] (b) (6), when a serum pregnancy test returned positive (reported level was 221). Ultrasound performed in the emergency room could not confirm the presence of an intrauterine pregnancy; she was instructed to return every other day for serum HCG and rule/out ectopic work-up. The second serum HCG level done on May 3, 2011 returned 324.

Follow-up information was obtained from the patient on June 1, 2011, when she confirmed having had an intrauterine pregnancy and reported having experienced a miscarriage on approximately May 11, 2011. Her vaginal bleeding resolved on May 31, 2011.

Medical officer comment:

The MedDRA term “ectopic pregnancy” assigned to this case is not appropriate since the pregnancy was confirmed to be intrauterine. Again, the miscarriage is related to pregnancy rather than to Plan B One-Step.

Case# 7938520 (ISR# 7470201): This is female (age unknown) whose LMP began on March 30, 2011. She took Plan B One-Step on April 10, 2011. On May 2, 2011, a pregnancy test was done at a clinic and was positive. An ultrasound done at the clinic reportedly showed an intrauterine pregnancy. She began to experience vaginal bleeding while in the clinic and was advised that she was having a miscarriage. No additional information was reported; the outcome of this pregnancy is not related to Plan B One-Step.

Case# 7955456 (ISR# 7496541): This is a 34-year-old female whose LMP began on April 10, 2011. Her medical history includes rheumatoid arthritis, for which she was taking prednisone. She reported two episodes of unprotected intercourse within the month prior to this report (filed on May 15, 2011); one dose of Plan B One-Step was reportedly taken after each of these two episodes. On May 13, 2011, the same day of her third episode of unprotected intercourse, she took Plan B One-Step. One hour and a half after taking Plan B One-Step, she reported experiencing heartburn and vomiting; both events resolved on the same day. She also reported that there appeared to be blood in the vomit, although she could not be sure if the appearance of blood could be attributed to the ketchup she had during dinner. In addition, she reported experiencing cramping and feeling tired on May 14, 2011; both of these events also resolved on the same day. This report was not medically confirmed; the event hematemeses was not definitely documented. Therefore, causality cannot be established.

Case# 7978772 (ISR#s 7529999 and 7543248): This report is from a female consumer whose age and LMP were unknown. She reported having unprotected sexual intercourse and taking Plan B One-Step on an unspecified date. She reported that she “passed out” on an unspecified date. The duration for her loss of consciousness was not specified. A follow-up report was sent

by the applicant to FDA six days after the initial report, upgrading the event to “serious.” No additional information was available. This report was not medically confirmed; causality of reported events cannot be attributed to Plan B One-Step.

Case# 7979654 (ISR#7531309): This is a report received from the husband of a female (age, LMP unknown) who took Plan B One-Step on an unspecified date following unprotected intercourse. It was reported that the consumer woke up “in a pool of blood” on an unspecified date. No additional information was available. Again, causality in this case cannot be determined.

Case# 7987957 (ISR# 7543269): This is a 44-year-old female whose LMP began on April 1, 2011. The reporter believed that she had been administered Plan B One-Step unknowingly in her coffee the morning of June 2, 2011. Approximately six hours after ingesting the coffee, she reported experiencing vomiting, vaginal bleeding, abdominal cramps and “stomach swelling.” She presented to two different emergency rooms (ER) in the course of two days for evaluation of her symptoms. Both times she was discharged on the same day of her ER visits; pregnancy tests were performed and returned negative. She surmised that Plan B One-Step may have caused her symptoms following an internet search, based on the constellation of her complaints.

Medical officer comment:

The relevance of this case to the present review is unclear, considering that the absence of medical confirmation or substantiation that Plan B One-Step was indeed ingested by the reporter. The MedDRA term “gastric dilatation” used to code her complaint of “stomach swelling” is not appropriate, since the history given is more indicative of a subjective feeling of bloating by the reporter. There was no suggestion of any gastric dilatation procedure having been performed in the report. The relationship between reported events and Plan B One-Step cannot be established.

Case# 8006719 (ISR# 7568694): This is a 20-year-old female whose LMP began on May 6, 2010. Her medical history was significant for anxiety. She reported taking Plan B One-Step for emergency contraception on May 27, 2010. Two home urine pregnancy tests performed on June 12, 2010 were positive. She reported experiencing light vaginal bleeding on June 12, 2010, and the bleeding became heavier the next day. She was evaluated by her physician on June 14, 2010 and was advised that she was having a miscarriage. No additional information was provided; the pregnancy outcome is unrelated to Plan B One-Step.

Case# 8008604 (ISR#s 7571443 and 7611006): This is a 40-year-old G₃P₁₀₁₁ female whose LMP, menstrual frequency and duration were unknown. She reported taking Levonelle (levonorgestrel 1.5 mg tablet) in 2011 when she was pregnant. She reported that she decided to terminate the pregnancy which would have taken place on May 16-2011. However, she experienced a miscarriage on June 5, 2011, at which time she would have been at approximately 9 weeks in gestation.

Follow-up information was obtained from her physician, who confirmed that a pregnancy test done on May 3, 2011 was positive. An ultrasound performed on June 6, 2011 confirmed miscarriage. No additional information was available. Causality of this outcome cannot be attributed to Plan B One-Step.

Case# 8010310 (ISR#s 7573954, 7588845, 7649213): This case was reported in literature.²² The patient is a 22-year-old Spanish female who developed venous thrombosis three days after taking Postinor (levonorgestrel 1.5 mg tablet) for post-coital contraception. Her past medical history included epistaxis associated with taking acetaminophen. She is also a fine arts student, and her daily routine included having her arms in fixed positions several hours per day for sculptures and painting.

She presented for care with pain and inflammation in her right upper arm, lasting approximately 24 hours in duration. Physical examination was noted for edema in the arm and pain on compression of her brachial musculature. A venous Doppler ultrasound revealed occlusive thrombosis; the findings were also confirmed by magnetic resonance venography (MRV). She commenced a six-month regimen of anticoagulation; a follow-up (MRV) showed full restoration of permeability in the affected region.

The authors concluded that both levonorgestrel and the postural stresses incurred by her professional activity contributed to the thrombosis. The reader is referred to section 7, Safety Summary, for additional discussion and analysis regarding this case.

Case# 7992390 (ISR#s 7549643 and 7780766): This is a female of unknown age who reported taking Levonelle (levonorgestrel 1.5 mg tablet) in March 2011 for emergency contraception. On May 12, 2011, she was reportedly almost 7 weeks pregnant by ultrasound. On June 6, 2011, she experienced a miscarriage. No additional information was available and no medical confirmation was received. Again, the pregnancy outcome is not deemed to be related to Plan B One-Step.

In addition to these 11 cases with serious outcomes, this PADER also includes 1,595 medically unconfirmed cases with outcomes classified as non-serious. Of these 1,595 cases, 1,276 cases (80%) identified adverse events (AE) which are already included in the current label. The most commonly reported AEs were menstrual irregularities (965 counts of 2,787 total AE counts), pelvic pain (185 counts of 2,787), nausea (177 counts of 2,787), and vomiting (128 counts of 2,787). Cases reporting unlabeled, non-serious AEs (318 cases) were largely associated with non-specific consumer complaints without discernable patterns.

Among these reports classified as non-serious, two appeared to be associated with notable adverse events based, at first glance, on the events coded. However, upon close examination, both cases are deemed to have been miscoded.

Case# 7939567 (ISR#7471716) – angina pectoris

This was reported by a female consumer who took Plan B One-Step for emergency contraception. Her age and menstrual histories are unknown. She reported experiencing “heart pain” on an unspecified date. No additional information was available. Coding this case with the MedDRA term “angina pectoris” is clearly inappropriate.

Case# 7887610 (ISR# 7397395) – hallucination

This reported was filed by the boyfriend of a female (age and LMP unknown) who took Plan B One-Step on an unspecified date. It was reported that the patient experienced hallucinations on an unspecified date. No additional information was available. The relevance of this report to the safety profile of Plan B One-Step, based on a secondary source, is doubtful.

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Table 6. Summary of 15-day reports received by Teva during the quarter of April 1, 2011 to June 30, 2011

AERS Case #	AERS ISR #	Teva Case#	Age	FDA received date	Event date	Source	Outcome	Adverse events (MedDRA PT)
7894914	7408410	241818USA	26	July 19, 2010 April-12-2011	August-10-2010	Consumer	OT	Abortion spontaneous, drug ineffective, pregnancy after post-coital contraception, vaginal hemorrhage, pelvic pain
7930290	7458205 7470195 7531092	279450USA	23	May-4-2011 May-10-2011 June-8-2011	May-11-2011	Consumer	OT	Ectopic pregnancy*, nipple pain, back pain, ovarian disorder, vaginal hemorrhage, pelvic pain, abortion spontaneous, drug ineffective, pregnancy after post-coital contraception
7938520	7470201	280634USA	?	May-10-2011	May-2-2011	Consumer	OT	Abortion spontaneous, drug ineffective, pregnancy after post-coital contraception, vaginal hemorrhage, nausea
7955456	7496541	281863USA	34	May-23-2011	May-13,14-2011	Consumer	OT	Hematemesis, dyspepsia, ovulation pain, vomiting, fatigue
7978772	7529999 7543248	284855USA	?	June-7-2011 June-13-2011	Unknown	Consumer	OT	Loss of consciousness
7979654	7531309	284358USA	?	June-8-2011	Unknown	Consumer	OT	Hemorrhage
7987957	7543269	284926USA	44	June-13-2011	June-2-2011	Consumer	OT	Abdominal pain upper, gastric dilatation**, menstruation irregular, vomiting
8006719	7568694	286771USA	20	June-23-2011	June-12-2010	Consumer	OT	Abortion spontaneous, anxiety, drug ineffective, menstruation irregular
7992390	7549643 7780766	285459ISR	?	June-15-2011 Sept-27-2011	June-6-2011	Consumer	OT	Abortion spontaneous, pregnancy after post-coital contraception, maternal exposure during pregnancy
8008604	7571443 7611006	286798ISR	40	June-24-2011 July-15-2011	June 5-2011	Consumer	OT	Abortion spontaneous, maternal exposure during pregnancy
8010310	7573954 7588845 7649213	285457ISR	22	June-27-2011 July-5-2011 August-2-2011	Unknown	literature	HO	Deep vein thrombosis

PT: preferred term

OT: other definition for serious outcome designated by the applicant

*the term ectopic pregnancy was inappropriately applied in this case

**the term gastric dilatation was inappropriately applied in this case

Blue: foreign cases

PADER 2: covering the period from July 1, 2011 to September 30, 2011

This safety report summarized 1,576 cases received by the applicant. There is no indication of any new safety concerns raised by these reports.

Among the 1,576 cases, eight cases were identified by the applicant as associated with serious outcomes warranting expedited 15-day reporting to AERS. Two of these cases (AERS case#s 8010310, 8008604 listed in Table 6) were already included in the PADER 1 discussed above. The remaining six new cases (five domestic and one foreign) were all spontaneous, consumer-generated reports and are summarized in Table 7 and a brief narrative summary of each case appears below:

Case# 8081514 (ISR# 7670850): This is a female (age and LMP unknown) who reported her pregnancy after taking Plan B One-Step. She reported that she developed a subchorionic hemorrhage, which resolved. The pregnancy was ongoing as of August 1, 2011. No other information was provided. This case was not medically confirmed.

Medical officer comment:

Subchorionic bleeding is a commonly observed during the first trimester of pregnancy; it frequently resolves spontaneously and has no adverse impact on pregnancy outcome. The event is not related to Plan B One-Step.

Case# 8018445 (ISR# 7711990): This report was received from the boyfriend of a female consumer (age and LMP unknown) who took Plan B One-Step on an unspecified date. On August 18, 2011, the reporter stated that his girlfriend had been vomiting blood and had had blood in her urine for at least 24 hours. No other information was provided; this medically unconfirmed case, based on a secondary reporting source, provides insufficient information to render a determination on relationship of the complaints to the product.

Case# 8136356 (ISR# 7751045): This is a 20-year-old female whose LMP began on May 5, 2010. She reported taking Plan B One-Step on May 27, 2010; timing of her taking the drug was within eight hours of unprotected intercourse. A home urine pregnancy test performed on June 12, 2010 was positive. A serum HCG level obtained on June 14, 2010 was reportedly “low,” prompting a work-up for ectopic pregnancy. The work-up was discontinued when HCG returned zero in July 2010. She reported that her healthcare provider informed her she had had a miscarriage. The outcome of miscarriage is unrelated to Plan B One-Step.

Case# 8138094 (ISR#s 7753517 and 7783936, mother) and Case# 8138098 (ISR# 7753521 and 7783937, baby girl):

These linked cases concerned a mother/baby pair. The mother is a 30-year-old female (LMP unknown) who took Plan B One-Step, unaware that she was already about four weeks pregnant. Her pregnancy was reportedly complicated by placenta previa, low amniotic fluid volume, diagnosed at approximately four months in gestation. The ultrasound also detected irregular fetal heart rate and cleft palate in the fetus. Labor was induced two weeks before her estimated due date and she delivered a baby girl vaginally on [REDACTED] (b) (6).

The infant weighed seven pounds at birth. The irregular heart rate reportedly resolved after birth. At six months of age, the baby underwent surgery to repair the cleft palate.

No additional relevant information was obtained despite the applicant's effort to reach the reporter for follow-up. This pair of cases was not medically confirmed.

Medical officer comment:

Induction of labor is contraindicated in the presence of known placenta previa. In this case, the placentation at the initial growth ultrasound at four months gestation was likely low-lying; resolution of the previa with advancing gestation enabled her to have a vaginal delivery. The apparently normal birth weight of the infant girl at 38 weeks gestation suggests that any abnormality in placentation or amniotic fluid level, did not adversely impact the pregnancy outcome. Thus, it appears that all reported events in this resolved, with exception of the congenital orofacial anomaly. Here, an association between the cleft palate and Plan B One-Step cannot be established. Congenital anomalies occur not uncommonly, and cleft lip with and without cleft palate is one of the most frequently observed congenital abnormalities (7.75 per 10,000 live births) in the United States.⁴⁵

Case# 8104241 (ISR#s 7706722 and 7759275): This is a 31 year-old female with a history of hepatitis and fibrosis of the liver. She reported taking Levonelle (levonorgestrel 1.5 mg tablet) on July 4, 2011. Pregnancy was diagnosed on an unspecified date, and she experienced a miscarriage on an unspecified date. This case was not medically confirmed and this pregnancy outcome is unrelated to Plan B One-Step.

In addition to these 6 cases classified with serious outcomes, this PADER also includes 1,570 medically unconfirmed cases with outcomes classified as non-serious. Of these 1,570 cases, a great majority of cases (1,249 cases, 80%) identified adverse events (AE) which are already included in the current label. The most commonly reported AEs in this report again were menstrual irregularities (978 counts of 2684 total AE counts), nausea (167 counts of 2684), pelvic pain (158 counts of 2684), and vomiting (139 counts of 2684). Cases reporting unlabeled, non-serious AEs (321 cases) were largely associated with non-specific consumer complaints without discernable patterns.

Among these reports classified as non-serious, some cases appeared to be notable on face. However, these were either clearly miscoded (ISR# 7652727, thrombosis coded for blood clots per vagina) or lacked sufficient clinical detail to render judgment on the clinical significance or the causality (ISR# 7737380, chest pain and ISR# 7790622, chest discomfort).

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Table 7. Summary of 15-day reports received by Teva during the quarter of July 1, 2011 to September 30, 2011

AERS Case #	AERS ISR #	Teva Case#	Age	FDA received date	Event date	Source	Outcome	Adverse events (MedDRA PT)
8081514	7670850	294437USA	?	Aug-9-2011	Aug-1-2011	Consumer	OT	Drug ineffective, pregnancy after post-coital contraception, subchorionic hemorrhage
8018445	7711990	297095USA	?	Aug-26-2011	Aug-18-2011	Consumer	OT	Hematemesis, blood urine present
8136356	7751045	300130USA	20	Sept-14-2011	June-12-2010	Consumer	OT	Abortion spontaneous, drug ineffective, pregnancy after post-coital contraception
8138094	7753517 7783936	300564USA	30	Sept-15-2011 Sept-28-2011	Oct-18-2010	Consumer	OT	Placenta previa, amniotic fluid volume decreased, maternal drug exposure during pregnancy, live birth
8138098	7753521 7783931	300581USA	0	Sept-15-2011 Sept-28-2011	Oct-18-2010	Consumer	CA, OT	Congenital oral malformation, fetal heart rate disorder, maternal drug exposure during pregnancy
8104241	7706722 7759275	296851ISR	31	Aug-24-2011 Sept-19-2011	Not specified	Consumer	OT	Abortion spontaneous, pregnancy after post-coital contraception, maternal drug exposure during pregnancy

PT: preferred term

OT: other definition for serious outcome designated by the applicant

Blue: foreign cases

PADER 3: covering the period from October 1, 2011 to December 31, 2011

This safety report summarized 1,290 cases received by the applicant. Among the 1,290, 12 cases meeting expedited reporting criteria were received by the applicant. Seven of the 12 were domestic in origin, while five were foreign cases. These 12 cases are summarized in Table 8 and brief narratives are provided below:

Case# 7910461 (ISR#s 7431662 and 7910461): This is a 20-year-old female (LMP unknown) who took Plan B One-Step on January 8, 2011. A home urine pregnancy test performed on February 4, 2011 was positive. On unspecified dates in February 2011, she had brief episodes of nausea and vaginal spotting, which resolved. She sought treatment in [REDACTED] (b) (6) for severe abdominal cramping and vaginal bleeding at an emergency room, where an ultrasound showed fetal demise with an absence of fetal heart rate. She reported undergoing a dilatation and curettage (D&C) at 13 weeks gestation on an unspecified date in [REDACTED] (b) (6). This case was not medically confirmed. The pregnancy outcome is unrelated to Plan B One-Step.

Case# 8160410 (ISR#s 7784242 and 7795375): This is a 19-year-old female whose LMP began on September 15, 2011. She reported having unprotected sexual intercourse on September 17, 2011 and took Plan B One-Step on September 20, 2011. Five days later, on September 25, 2011, she experienced loss of vision for 10 seconds, as well as vaginal bleeding and dizziness, both of which resolved within one day. She also reported experiencing numbness in the two distal fingers of her left hand on September 26, 2011; the numbness did not resolve as of September 27, 2011. No additional clinical information was available. It is unclear whether she sought medical attention for the symptoms. Causality cannot be determined given limited information.

Case# 8179501 (ISR# 7812133): This is a female (age and LMP unknown) who took Plan B One-Step on October 9, 2011 following unprotected intercourse. She reported “vomiting blood” five minutes after taking Plan B one-Step. No other information is available. There was no information on the amount of blood in the vomit or whether she sought medical care. Causal relationship to Plan B One-Step cannot be established.

Case# 8208707 (ISR# 7867779): This is a female (age and LMP unknown) who took Plan B One-Step on October 24, 2011. She reported passing out approximately four hours after taking the product. No other clinical information was available. Assessment of causality is not feasible due to insufficient information.

Case# 8255292 (ISR# 7928322): This is a female (age unknown) whose LMP started on October 25, 2011. She took Plan B One-Step on November 5, 2011 following unprotected intercourse. She experienced vaginal bleeding from November 7 to 10, 2011, and much heavier bleeding for a few hours on November 12, 2011 after a second act of intercourse. She did not specify whether any contraception method had been used with the second act of intercourse. Additionally, she experienced nausea and vomiting on November 12, 2011. She reported possibly seeing blood in the vomit but no blood was seen in the toilet bowl. No additional clinical information was available. There is no medical confirmation of hematemesis; causality of unconfirmed hematemesis cannot be assigned to Plan B One-Step.

Case# 8258479 (ISR# 7932864): This is a female (age and LMP unknown) who had unprotected intercourse on an unspecified date in August 2011. She reported taking Plan B One-Step more than 72 hours after the episode. A home urine pregnancy test performed in August 2011 (date unspecified) was positive. She subsequently went to an emergency room on an unspecified date in [REDACTED] (b) (6) seeking treatment for severe low back pain. Serum pregnancy test returned negative in the ER. She was advised that she had had a miscarriage. Her low back pain resolved on an unspecified date. No additional information was available. The pregnancy outcome is unrelated to Plan B One-Step.

Case# 8313928 (ISR# 8011430): This is a female (age and LMP unknown) who took Plan B One-Step on December 23, 2011. She reported that she vomited blood from December 23 into December 24, 2011. No additional clinical information was available. The amount of blood and vomiting is not specified. This report is not medically confirmed. Insufficient information provided in the narrative in this case precludes an assessment of causality or relationship with the product.

Case# 8158324 (ISR#s 7781215, 7800190, 7825439, and 7901098): This is literature report concerning a 23-year-old G₈P₁₀₇₁ female from Spain who experienced a cerebrovascular accident. The patient has a medical history of migraine without aura. Her obstetrical history is notable for seven miscarriages in the first and second trimester of pregnancy; she is the mother of one healthy child born at term. Her family history is significant for her mother having a stroke at age 45 and her sister having repeated first trimester miscarriages.

The patient took Postinor (levonorgestrel 1.5 mg tablet) on August 7, 2009 for emergency contraception. She then experienced reduced strength and sensitivity in the right side of her body upon awakening the next morning. She was seen at an emergency room [REDACTED] (b) (6) after the onset of symptoms; a neurological examination showed mild nominative aphasia, diplopia compatible with pseudoparesis of the 4th right cranial pair, right hemifacial hypoesthesia and right hemiparesis. Cerebral CT and MRI showed cerebral infarction in the left anterior thalamus. A transesophageal echocardiogram was negative. Hypercoagulability work-up, including anti-phospholipid antibodies, factor V Leiden mutation, prothrombin gene mutation, protein C and S deficiencies, was negative. No concomitant medications were reported. She recovered from these reported events on October 28, 2009. The reader is referred to additional discussion and analysis for this case in section 7, Safety Summary above.

Case# 8195648 (ISR# 7834017): This report was forwarded to the applicant by the Irish Medicines Board on October 12, 2011. The report concerned a 21-year-old female (LMP unknown) who took Levonelle (levonorgestrel 1.5 mg tablet) on September 1, 2011 following an episode of unprotected intercourse. On September 4, 2011, three days after taking the product, the consumer reportedly had Henoch-Schönlein purpura (HSP). There were no concomitant medications reported, and no treatment was administered. She reportedly recovered from the event at the time of report. It is unclear whether this case had been medically confirmed prior to being reported to the Irish Medicines Board.

Medical officer comment:

While the reported clinical course is consistent with the self-limiting nature of HSP, it is unknown whether the diagnosis was supported by a rash or established by confirmatory skin biopsy. HSP is a vasculitic syndrome of unknown etiology; one report three days following ingestion of a drug is not adequate to establish a causal link.

Case# 8258621 (ISR#s 7933056 and 7990954): This is a spontaneous report from a 33-year-old British female who has been attempting to conceive for approximately one year. Her medical history is notable for chronic depression for which she has been on Effexor (venlafaxine). She denied having taken any other type of hormonal contraception. She stated that her fertility tests were “normal” but added that her “uterine lining is not thickening enough.”

On November 4, 2011, she stated that since she last took Levonelle (levonorgestrel 1.5 mg tablet) in 2006, her periods had become lighter and shorter (lasting only one to two days) but still regular. She reportedly took Levonelle eight times over six years between 2000 and 2006 for emergency contraception; no more than one dose had been taken within the same month. This report is not medically confirmed, and there is insufficient clinical information to render an adequate assessment on the relationship between reported events and levonorgestrel.

Medical officer comment:

The consumer did not report her weight. It is unclear whether she is an avid exerciser or if she had anorexia associated with her depression, as very athletic women or women of low body mass index often have menstrual irregularities.

The use of contraceptive methods, with the exception of male and female sterilization, does not result in an irreversible change in fertility.³⁶ In a woman who does not have other underlying etiologies for infertility, ovulatory function (hence fertility) resumes quickly upon discontinuation of oral contraceptive pills (which act primarily by inhibiting ovulation). The same would be expected with emergency contraceptive products. A potential relationship between episodic ingestions of levonorgestrel five years prior and the purported current difficulty to conceive appears doubtful.

Case# 8261341 (ISR#7936971): This is spontaneous report from the U.K. concerning a female of unknown age. The consumer took Levonelle (levonorgestrel 1.5 mg tablet) on an unspecified date in August 2010. She subsequently experienced shortened menstrual cycle and symptoms of urinary tract infection (dysuria). No additional information was available. This case is not medically confirmed.

Medical officer comment:

The urinary symptoms are more likely attributed to the act of sexual intercourse rather than to levonorgestrel.

Case# 8275897 (ISR# 7958690): This report was from a physician in Romania conducting a non-Teva sponsored clinical trial. The report concerned a 39-year-old female who took Plan B

One-Step on October 15, 2011. On November 12, 2011, a urine pregnancy test was positive. Incomplete abortion (at 7 weeks gestation) was diagnosed via ultrasound on November 14, 2011. A dilatation and curettage (D&C) was recommended. The outcome was not specified in this case. The physician did not assess causality.

Medical officer comment:

Levonorgestrel EC is not 100% effective in preventing pregnancy. The event of incomplete abortion and subsequent need for D&C were related to the pregnancy, rather than to Plan B One-Step specifically.

In addition to these 6 cases classified with serious outcomes, this PADER also includes 1,278 medically unconfirmed cases with outcomes classified as non-serious. Of these 1,278 cases, a great majority of cases (1014 cases, 79%) identified adverse events (AE) which are already included in the current label. As with the two other PADERs, the most commonly reported AEs in this report were menstrual irregularities (802 counts of 2,271 total AE counts), nausea (152 counts of 2,271), pelvic pain (138 counts of 2,271), and vomiting (98 counts of 2,271). Cases reporting unlabeled, non-serious AEs (264 cases) were largely associated with non-specific consumer complaints without discernable patterns.

Among these reports classified as non-serious, some cases appeared to be notable on face. For example, ISR# 7807613 coded “palpitation” and “hypertension” based on verbatim report of “heart racing and high blood pressure,” ISR# 7830312 reported spontaneously resolved “chest pain and vision blurred,” ISR# 7889061 coded “chest pain and feeling hot,” ISR# 7953117 coded “ovarian infection” based on consumer’s own assessment, and ISR# 8000586 miscoded blood clots as “thrombosis.” However, none of these cases were confirmed by healthcare providers and the scant details available preclude an adequate assessment of relationship.

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Table 8. Summary of 15-day reports received by Teva during the quarter of October 1, 2011 to December 31, 2011

AERS Case #	AERS ISR #	Teva Case#	Age	FDA received date	Event date	Source	Outcome	Adverse events (MedDRA PT)
7910461	7431662 7928176	266740USA	20	April-22-2011 Nov-18-2011	March-?-2011	Consumer	OT	Abortion spontaneous, drug ineffective, menstruation irregular, nausea, pregnancy after post-coital contraception, vaginal hemorrhage, abdominal pain
8160410	7784242 7795375	302778USA	19	Oct-4-2011	Sept-25-2011	Consumer	OT	Blindness, hypoesthesia, menstruation irregular, dizziness
8179501	7812133	304489USA	?	Oct-13-2011	Oct-9-2011	Consumer	OT	hematemesis
8208707	7867779	306750USA	?	Oct-28-2011	Oct-24-2011	Consumer	OT	Loss of consciousness
8255292	7928322	309048USA	?	Nov-18-2011	Nov-12-2011	Consumer	OT	Hematemesis, menstruation irregular, nausea, coital bleeding
8258479	7932864	309704USA	?	Nov-22-2011	Sept-?-2011	Consumer	OT	Abortion spontaneous, back pain, pregnancy after post-coital contraception, off-label use
8313928	8011430	314959USA	?	Dec-28-2011	Dec-23, 24-2011	Consumer	OT	Hematemesis
8158324	7781215 7800190 7825439 7901098	302240ISR	23	Sept-27-2011 Oct-6-2011 Oct-19-2011 Nov-8-2011	Aug-8-2009	Literature	HO	Cerebrovascular accident
8195648	7834017	305389ISR	21	Oct-24-2011	Sept-4-2011	Health authority	OT	Henoch-Schölein purpura
8258621	7933056 7990954	309122ISR	33	Nov-22-2011 Dec-19-2011	Nov-22-2011 Dec-19-2011	Consumer		Infertility female, menstrual disorder, endometrial disorder
8261341	7936971	309805ISR	?	Nov-23-2011	Aug-?-2010	Consumer	OT	Urinary tract infection, polymenorrhea
8275897	7958690	311432ISR	39	Dec-6-2011	Nov-14-2011	Physician	OT	Abortion spontaneous, abortion incomplete, maternal drug exposure during pregnancy

PT: preferred term

OT: other definition for serious outcome designated by the applicant

Blue: foreign cases

PADER 4: covering the period from January 1, 2012 to March 31, 2012

This safety report summarized 1,486 cases received by the applicant during this reporting period. Among these 1,486 cases, 12 met the expedited reporting criteria and were classified as having serious outcomes by the applicant. Of these 12 cases, eight were domestic in origin, and the remaining four were foreign cases. Two of the 12 cases are linked and discussed together below since they concern a mother-baby pair. This PADER does not indicate any new potential safety issues. These 12 cases with serious outcomes are summarized in Table 9 and brief narratives are provided below:

Case# 7847897 (ISR#s 7340828, 8025341, and 8044874): This is a 21-year-old female whose LMP was January 26, 2011. She had unprotected intercourse on February 16, 2011 and took Plan B One-Step on February 17, 2011. A home pregnancy test done on March 4, 2011 was positive. No follow-up information was available until the applicant contacted the patient on January 4, 2012. The patient reportedly went for a routine ultrasound at 17 weeks gestation on June 3, 2011. No fetal heartbeat was found. She was told that the baby had been dead for two weeks. A confirmatory ultrasound was also performed at the hospital where the patient underwent labor induction. She was also diagnosed to have bacterial vaginosis, and was treated with “unknown pills.” She was discharged two days after the procedure.

Subsequently, the applicant received the patient’s medical records on January 9, 2012. The records confirmed that she had been seen at the clinic at 17 weeks gestation on June 3, 2011. On examination, the fundal height was not appropriate for gestation age and fetal heart tone was absent on Doppler and by clinic ultrasound. She was admitted to the hospital on (b) (6) due to fetal demise and received misoprostol for labor induction. Following an uncomplicated vaginal delivery, she was discharged in stable condition on (b) (6). Three days later, on (b) (6), the patient presented to the emergency room with complaints of vaginal bleeding, contraction type pain and nausea. On examination, she was febrile, with a temperature of 102.8°F. Available AERS report did not specify what treatment she received, or her clinical course in the emergency room/hospital.

Medical officer comment:

The pregnancy-related adverse outcomes in this case cannot be imputed to Plan B One-Step. There are numerous potential etiologies for second-trimester pregnancy losses. It is unclear whether diagnostic work-up for the loss was done.

Based on the medical records, this patient’s postpartum course appeared to have been complicated by postpartum endometritis, manifested by fever and increased bleeding/cramping. It is likely that bacterial vaginosis was a contributing factor in her infection.

Case# 7876612 (ISR#s 7381959, 8060646, 8067696, and 8114130): This is a 26-year-old female whose LMP began on February 24, 2011. She reportedly had unprotected intercourse and took Plan B One-Step on March 12, 2011. Home urine pregnancy tests performed on March 23, 2011 and March 26, 2011 were both positive. She reported these events to the applicant on March 26, 2011. Follow-up information was obtained by the applicant on January 13, 2012.

The patient reportedly had an ultrasound on an unspecified date in March 2011; the ultrasound confirmed that the pregnancy was not viable. She underwent a dilatation and curettage.

The applicant obtained her medical records on January 31, 2012 for review. Her LMP was stated as February 22, 2011. Her medical history was notable for depression and allergies. She was seen at the clinic on April 5, 2011, with a complaint of daily cramping for one week. Vaginal ultrasound on April 5, 2011, when her gestational age would have been 6 weeks based on LMP, revealed no fetal pole or heart tone. At this time, her quantitative human chorionic gonadotropin (HCG) was 31,544 mIU/ml. The high level of quantitative HCG in the face of an empty gestational sac prompted a work up for gestational trophoblastic disease. The quantitative HCG was repeated two days later, on April 7, 2011, and returned 54,691 mIU/ml. An ultrasound performed on April 8, 2011 again showed no embryo or heart tone. She underwent a dilatation and curettage on [REDACTED] without complications. Chorionic villi were seen on histology; thus molar pregnancy was ruled out. Her post-D&C HCG levels obtained on May 3, 2011 and June 2, 2011 were both < 5 mIU/ml.

Medical officer comment:

Again, the adverse outcome here is related to pregnancy, not Plan B One-Step per se.

Case# 8352021 (ISR# 8067702): This is a spontaneous report from a 13-year-old female (LMP unknown) who took Plan B One-Step for emergency contraception on an unspecified date in 2011. She reported experiencing lower, right-sided abdominal pain and shoulder pain on an unspecified date in September 2011. A urine pregnancy test and a serum pregnancy test performed on an unspecified date in September 2011 were positive. Although her healthcare provider considered ectopic pregnancy a possibility (given the unilateral abdominal pain and shoulder pain), the provider was not able to confirm pregnancy to be extrauterine. The patient reportedly miscarried in September 2011, with resolution of all her symptoms. No additional information was available.

Medical officer:

Based on the narrative, this case was inappropriately coded as an ectopic pregnancy.

Case# 8355182 (ISR# 8071918): This is a spontaneous report from a 22-year-old female whose LMP began on December 16, 2011. She had unprotected intercourse on January 14, 2012 and took Plan B One-Step on January 15, 2012. She reported experiencing menses-like cramps on January 16, 2012, and profuse vaginal bleeding on January 17, 2012. By January 18, 2012, she reportedly had used two and a half boxes of 18-count tampons and one box of 20-count sanitary pads, prompting her to contact her healthcare provider. The provider prescribed iron supplement and gave the patient an appointment for follow-up on January 19, 2012. No additional information was available.

Medical officer comment:

Irregular bleeding (in timing or amount) is already a labeled event for levonorgestrel EC. Furthermore, additional medical information is not available to assess whether the reported

heavy vaginal bleeding was clinically significant. For example, there is no indication that her vital signs had become unstable or that she developed anemia as a result of the vaginal bleeding.

Case# 8386731 (ISR# 8109378): This is a spontaneous report from a 31-year-old female whose LMP began on December 24, 2011. She reportedly had unprotected intercourse on January 3 and 4, 2012, and took Plan B One-Step on January 7, 2012. A home urine pregnancy test performed on January 17, 2012 was positive. Urine and serum pregnancy tests were subsequently performed at a doctor's office on January 23, 2012 and both were positive. A transvaginal ultrasound performed on January 23, 2012 reportedly showed her gestation to be "four weeks and two days" but did not show a sac. Reportedly, the patient was advised by her provider that her uterine lining was half the thickness of what is expected for a gestational age of four weeks and two days. The reported events were not medically confirmed and no additional information is available.

Medical officer comment:

In this case, Plan B One-Step was taken beyond the 72-hour therapeutic window per the label. Coding this case as "off-label use" is appropriate. Nevertheless, as I have repeatedly stated, her pregnancy reflects a known limit in the effectiveness of Plan B One-Step and is not indicative of a safety issue.

The estimated gestational age of four weeks two days is based solely on her LMP. At this early gestational age, transvaginal ultrasound is not expected to demonstrate the existence of a fetal pole or embryonic heart tone. Therefore, the status of her pregnancy is yet undetermined. That is to say, it is unclear whether she has an intrauterine vs. ectopic pregnancy, and if the pregnancy is intrauterine, whether it is viable. Without additional information, it is unclear what implication a purported decrease in endometrial thickness would have. The applicant's assessment that this case represents an "uterine disorder" and a "complication of pregnancy" is without merit.

Case# 8456738 (ISR# 8205981): This is a spontaneous report forwarded to the applicant by the manufacturer of generic version of Plan B. It concerns a 29-year-old female (LMP unknown) who took Plan B One-Step on an unspecified date. It was reported that the patient was later found to be pregnant and experienced a miscarriage. No additional information is available. Of note, there appears to be some discrepancy in the information provided. Under "patient information," the patient's age was noted as 29 years of age. However, in the appended narrative, the patient was said to be "age unknown."

Medical officer comment:

It is unclear which product the patient actually took since the report originated from the generic manufacturer. The generic manufacturer markets Plan B, not Plan B One-Step. There is insufficient information to adequately assess the events of this report.

Case# 8468379 (ISR#s 8222580, 8231233, 8245259, 8251237, and 8272980): This is a spontaneous case reported by a 19-year-old female whose LMP began on March 1, 2012. She

reportedly took Plan B One-Step on March 9, 2012 following unprotected intercourse the day before. On March 12, 2012, she reported experiencing lower abdominal pain and vaginal spotting. By March 15, 2012, the vaginal bleeding had become heavy. A home urine pregnancy test performed on March 19, 2012 was positive. The applicant's follow-up with this patient revealed that her bleeding had resolved by March 31, 2012. A home urine pregnancy test performed on April 1, 2012 was negative. There was no medical confirmation of the information described in this report. Her pregnancy outcome is unrelated to Plan B One-Step.

Case# 8479015 (ISR#s 8238849, 8245277, and 8272405): These are spontaneous reports from a now 32-year-old female who contacted the applicant about her 2009 miscarriage. She stated that she took Plan B One-Step on an unspecified date in 2009 but became pregnant. She experienced heavy vaginal bleeding at 12 weeks gestation in September 2009. She underwent a D&C for the miscarriage. No additional information was provided. Again, the adverse pregnancy outcome is unrelated to Plan B One-Step.

**Case# 8382279 (ISR# 8103190, mother) and
Case# 8382238 (ISR#s 8103113 and 8156519, baby boy):**

These linked cases concerned a mother/baby pair in Ireland. The mother is a 31-year-old female whose LMP began on January 29, 2011. She reportedly had unprotected intercourse on February 12, 2011 and took Levonelle One-Step (levonorgestrel 1.5 mg tablet) on February 13, 2011. She also reported that she had been intermittently taking domperidone and herbal preparations during the month prior to taking levonorgestrel EC, and questioned whether these preparations might have interfered with the efficacy of EC. Pregnancy was subsequently diagnosed and she indicated that the estimated delivery date was [REDACTED] (b) (6).

The applicant obtained medical confirmation from the patient's physician. On [REDACTED] (b) (6), the patient gave birth to a male infant weighing 3.18 kg via forceps delivery. The records indicated no maternal complication during pregnancy/delivery and no congenital abnormality in the infant. A Mongolian spot on the baby's left buttock was deemed to be unrelated to levonorgestrel EC by the reporting physician; I concur.

Medical officer comment:

The coded term "drug interaction" appears to be based on the consumer's conjecture rather than actual data. Mongolian spots are frequently observed in the newborn; any causal relationship with levonorgestrel is doubtful.

Case # 8436918 (ISR#s 8179265 and 8220504): This report is forwarded to the applicant by the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom. The report concerns a 17-year-old female who was hospitalized due to migraine. Her LMP was unknown, and her past medication included Microgynon (levonorgestrel and ethinyl estradiol) from July 30, 2011 to January 14, 2012 for an unknown indication. She experienced migraine on January 24, 2012. Concomitant medication included Femicept tablet (levonorgestrel 150 mcg/ethinyl estradiol 30 mcg, a generic product of Microgynon) since January 24, 2012. The

complaint of migraine was said to have resolved on an unspecified date. No additional information was available.

Medical officer comment:

The available narrative for this case contains few details, other than to indicate that the patient was on a combined oral contraceptive containing 150 mcg of levonorgestrel and 30 mcg of ethinyl estradiol in each tablet. Attribution of causality in this case is confounded by daily, concomitant administration of both estrogen and levonorgestrel.

Case# 8482386 (ISR# 8243664): This is a spontaneous report received by the applicant. It concerns a female patient of unknown age and LMP who experienced a miscarriage. She had had two successful pregnancies. She reportedly took Levonelle One-Step (levonorgestrel 1.5 mg tablet) within 48 to 72 hours of unprotected intercourse. Pregnancy was diagnosed on an unspecified date. When she presented for an ultrasound at 7 weeks gestation, findings indicated that she had had a miscarriage, and the fetus “failed to develop.” She reportedly underwent a surgical procedure for the treatment of miscarriage. No additional information was available. Her pregnancy outcome is unrelated to Plan B One-Step.

In addition to these 12 cases classified with having serious outcomes, this PADER contains 1,474 cases medically unconfirmed cases with outcomes classified by the applicant as non-serious. Of these 1,474, the majority (1,151 cases, 78%) identified AEs that are non-serious and already included in the label. The most commonly reported AEs in this report again were menstrual irregularities (918 counts of 2,693 total AE counts), nausea (166 counts of 2,693), pelvic pain (155 counts of 2,693), and vomiting (125 counts of 2,693). Again, cases reporting unlabeled and non-serious AEs (322 cases) were largely associated with non-specific consumer complaints without any discernable patterns.

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 Christina Chang, M.D., M.P.H.
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 Plan B One-Step (Levonorgestrel 1.5 mg)

Table 9. Summary of 15-day reports received Teva during the quarter of January 1, 2012 to March 31, 2012

AERS Case #	AERS ISR #	Teva Case#	Age	FDA received date	Event date	Source	Outcome	Adverse events (MedDRA PT)
7847897	7340828 8025341 8044874	269907USA	21	Mar-9-2011 Jan-5-2012 Jan-13-2012	June-3-2011	Consumer, Confirmed by medical records	HO	Abortion missed, vaginitis bacterial, pyrexia, streptococcus test positive, drug ineffective, pregnancy after post-coital contraception, fatigue menstruation irregular, pelvic pain, nausea
7876612	7381959 8060646 8067696 8114130	273569USA	26	Mar-29-2011 Jan-20-2012 Jan-24-2012 Feb-4-2012	April-5-2011	consumer	OT	Abortion missed, hormone level abnormal, back pain, drug ineffective, pregnancy after post-coital contraception, abdominal pain, nausea, dizziness
8352021	8067702	318036USA	13	Jan-24-2012	Sept-?-2011	Consumer	OT	Abortion spontaneous, ectopic pregnancy, musculoskeletal pain, abdominal pain lower
8355182	8071918	318216USA	22	Jan-26-2012	Jan-17, 18-2012	Consumer	OT	Vaginal hemorrhage, dysmenorrhea
8386731	8109378	319143USA	31	Feb-2-2012	Jan-23-2012	Consumer	OT	Complication of pregnancy, uterine disorder, pregnancy after post-coital contraception, off-label use
8456738	8205981	326156USA	29	Mar-13-2012	Unknown	Watson	OT	Abortion spontaneous, drug ineffective, pregnancy after post-coital contraception
8468379	8222580 8231233 8245259 8251237 8272980	328327USA	19	Mar-20-2012 Mar-23-2012 Mar-29-2012 Apr-2-2012 Apr-11-2012	Mar-15-2012	Consumer	OT	Abortion spontaneous, uterine hemorrhage, myalgia, abdominal pain lower, menstruation irregular, drug ineffective, pregnancy after post-coital contraception
8479015	8238849 8245277 8272405	329041USA	28	Mar-27-2012 Mar-29-2012 Apr-10-2012	Sept-?-2009	Consumer	OT	Abortion spontaneous, uterine hemorrhage, drug ineffective, pregnancy after post-coital contraception
8382279	8103190	286799ISR	31	Feb-1-2012	2011	Consumer	OT	Pregnancy after post-coital contraception, drug interaction
8382238	8103113 8156519	319558ISR	0	Feb-1-2012 Feb-22-2012	2011	Physician	CA	Congenital nevus, fetal exposure during pregnancy
8436918	8179265 8220504	324406ISR	17	Mar-2-2012 Mar-20-2012	Jan-24-2012	Health authority	HO	Migraine
8482386	8243664	330243ISR	?	Mar-29-2012	Unknown	consumer	OT	Abortion spontaneous, pregnancy after post-coital contraception, maternal drug exposure during pregnancy

PT: preferred term

OT: other definition for serious outcome designated by the applicant

Blue: foreign cases

9 Appendices

9.1 Literature Review

A total of 31 publications pertinent to levonorgestrel EC use in adolescents were summarized and reviewed in my October 5, 2011 review for the original submission to this supplemental application. These publications were wide-ranging in nature and included survey-type studies, controlled clinical trials, observational studies, meta-analyses, and review articles. An updated literature survey of peer-review articles published since October 2011 focusing on EC use in adolescent population yields one article that published the known results of DR-LEV-302.¹² The reported findings were consistent with the information provided by the applicant in the first review cycle.

The reader is referred to section 7, Safety Summary, for additional discussion pertaining to relevant literature on thromboembolism risks.

9.2 Labeling Recommendations

Many aspects of this proposed label were arrived at following labeling negotiation during the first review cycle for this supplement; these are reflected in the current Drug Facts label. The reader is referred to the labeling review, dated November 16, 2011 and the applicant's version of accepted labeling submitted on December 7, 2011 for the label that was agreed upon between FDA and the applicant during the first review cycle. In this CR, the applicant has amended the target population to limit OTC access to females aged 15 years and older. To highlight the proposed age restriction, a statement was added under the section headlined **Directions**: “(b) (4) Further, a box containing three bulleted statements is added to the space next to Drug Facts, calling attention to the restricted distribution plan. Refer to comment 3 below for further discussion.

Additionally, in pursuit of the full OTC status for females aged 15 years and older, the previous dual-label containing both Rx and OTC versions is no longer intended; the proposed label has deleted the Rx label entirely, leaving only the Drug Facts and Consumer Information Leaflet (CIL) portion. The amended labeling pertains to the Drug Facts only; no changes are proposed to the CIL. Detailed labeling review will be conducted by reviewers in the Division of Nonprescription Regulation Development (DNRD). I have the following comments on the proposed label submitted by the sponsor:

Pertaining to the Principal Display Panel (PDP) and Drug Facts on cartons intended for trade and clinic distribution:

1. The statement under the **Use** section, “reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control” has been changed to “for women to reduce chance of pregnancy after unprotected sex (if a contraceptive failed or

if you did not use birth control.” This change is acceptable; it is the language that would have been approved during the last review cycle.

2. Under the *Directions* section, the first bulleted statement has been changed from “women 17 years of age or older” to (b) (4). Correspondingly, the second major bulleted statement “prescription only for women younger than age 17. If you are younger than age 17, see a healthcare professional” has been deleted. This is also acceptable.
3. A box has been added to the area next to Drug Facts on the PDP and it contains three bulleted statements:
 - Not for sale to those under 15 years of age
 - Proof of age required
 - Not for sale where age cannot be verified.

The first bulleted statement, “Not for sale to those under 15 years of age,” is problematic, as it conveys a message that seems incongruent with the first proposed bulleted statement under *Directions*, (b) (4). The “Not for sale” statement will be perceived to be more restrictive than the (b) (4) statement, and it is not apparent to me which directions pharmacists will follow. It is unclear if pharmacists would dispense the product to an adolescent who is younger than 15 years of age, even if the adolescent presents a prescription for Plan B One-Step. A potential remedy may be to expand the statement to allow prescription use for those under 15 years of age in order to align the two instructions surrounding age restriction. The statement could be modified to read: “Not for sale to those under 15 years of age unless they have a prescription.”

The next two bulleted statements are likely intended to address the HHS Secretary’s concerns. The applicant has proposed a distribution plan modeled after that of the nicotine-containing nicotine replacement therapies (NRTs), which are restricted for OTC sale to consumers 18 years of age or older. The applicant has committed to limiting Plan B One-Step distribution to the Family Planning aisle of retail outlets with an on-site pharmacy, with an understanding that the product is available for sale during the retailer’s normal operating hours. Further, the applicant has arranged with retail outlets to implement an age-verification protocol, whereby scanning the UPC code of the product for purchase at the cash register would prompt the cashier to request proof of age from consumer. While I have no objections to these measures, I do not believe these steps are necessary.

4. Under the *Other information* section, the first bulleted statement has been changed to “read the instructions, warnings and enclosed product leaflet before use” from “before using this product read the enclosed consumer information leaflet for complete directions and information.” This change was agreed to during the previous review cycle and

would have appeared in the labeling had the December 7, 2011 FDA action not been overruled by HHS.

5. The second bulleted statement under *Other information*, “this product is not recommended for regular birth control. It does not work as well as most other birth control methods used correctly,” has been deleted. This is acceptable since there is already a bulleted statement “for regular birth control” under the section *Do not use*.
6. The fourth bulleted statement under *Other information*, “when used correctly every time you have sex, latex condoms greatly reduce, but do not eliminate, the risk of pregnancy and the risk of catching or spreading HIV, the virus that causes AIDS. See condom labeling for additional STD information,” has been deleted. This change was already agreed to during the previous review cycle, given the presence of a more prominent *Sexually transmitted diseases (STDs) alert* section near the beginning of the Drug Facts.
7. The fifth bulleted statement under *Other information*, “tablet is enclosed in a blister seal. Do not use if the blister seal is broken,” has been changed to “do not use if carton is open or tear strip is removed or blister seal is broken or missing.” This change is acceptable and was already agreed to previously.

9.3 Advisory Committee Meeting

Two Advisory Committee meetings have been convened to date where the deliberations are relevant to the topic of this review – the December 2003 joint session of the Nonprescription Drug Advisory Committee (NDAC) and the Advisory Committee for Reproductive Health Drugs (ACRHD), which discussed the original Plan B OTC switch application, and the January 2012 Pediatric Advisory Committee (PAC), which reviewed the Plan B One-Step postmarketing safety data in adolescents. The Committees’ votes and discussions are summarized below.

NDAC/ACRHD joint session in 2003 to discuss OTC switch of Plan B:

No advisory committee meeting was held for the current supplemental application because an advisory committee meeting in 2003 addressed Rx-to-OTC issues for the closely related product, Plan B. Because the committee opinions are relevant to the current application, a summary follows:

On December 16, 2003, FDA convened a joint session of the Nonprescription Drug Advisory Committee (NDAC) and the Advisory Committee for Reproductive Health Drugs (ACRHD) to discuss NDA 21-045, which sought OTC marketing of Plan B.⁴⁶

After reviewing the data submitted to support of full OTC availability, the joint Committee voted overwhelmingly in favor of the Rx-to-OTC switch of Plan B without age restriction. Questions posed to the Committee and the vote tallies were the following:

Question 1. Does the Actual Use Study (AUS) demonstrate that consumers used the product as recommended in the proposed labeling?

Yes = 27; No = 1; Abstain: 0

Question 2. Are the AUS data generalizable to the overall population of potential non-Rx users of Plan B?

Yes = 27; No = 1; Abstain: 0

Question 3. Based on the AUS and literature review, is there evidence that non-Rx availability of Plan B leads to substitution of emergency contraception (EC) for the regular use of other methods of contraception?

Yes = 0; No = 28; Abstain: 0

Question 4. Do the data demonstrate that Plan B is safe for use in the non-prescription setting?

Yes = 28; No = 0; Abstain: 0

Question 5. Are the plans for introduction of Plan B into the non-Rx setting adequate with respect to consumer access and safe use? If no, what other options would you recommend?

Yes = 22; No = 5; Abstain: 1

Question 6. Do you recommend Plan B be switched from Rx to non-Rx status?

Yes = 23; No = 4; Abstain: 0; (one member left before voting commenced)

Medical officer comment:

*Based on my review of the meeting transcript, there was one aspect of the Committee's deliberation that is pertinent to this supplemental application. Committee members who supported the OTC status switch by voting yes for question 6 endorsed the switch as proposed with respect to the age of target population. Furthermore, while most saw no need for any postmarketing studies, some members recommended **post-approval** studies in adolescents to assess their comprehension and contraceptive behavior since they supported approval with no age restriction. Data contained in this supplemental application serve as validation that the original dual marketing status action was unnecessary.*

Given that Plan B One-Step involves a simpler dosing regimen than Plan B, recommendations made by the 2003 Committee for OTC marketing apply to Plan B One-Step. Data contained in this application and in updated literature review have not presented evidence to contradict what was presented to the 2003 Advisory Committee. In fact, information collected from

postmarketing surveillance and literature since 2003 have strengthened the case for decreasing barriers to access for adolescents.

PAC meeting in 2012 to discuss Plan B One-Step postmarketing safety data in adolescents:

Postmarketing safety data in the pediatric population were presented and reviewed by the PAC on January 30, 2012. Such review is mandated by the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), which require the PAC to review of pediatric safety data 18 months following any product approval to assess the need for labeling revision based on postmarketing safety information. In this case, the PAC was presented pediatric adverse event data on levonorgestrel 0.75 mg tablet (Plan B and generics) and 1.5 mg tablet (Plan B One-Step) following the July 2009 approval for dually-labeled Plan B One-Step. The pediatric safety review was conducted by the Division of Pharmacovigilance II (DPV II) in the Office of Surveillance and Epidemiology (OSE), and assessed reports received by FDA from January 1, 2002 to December 31, 2010. Upon reviewing AERS reports concerning adolescents 17 years and under, OSE concluded there was no evidence of pediatric safety concerns with levonorgestrel EC.⁴⁷ I was in attendance at this PAC meeting, and witnessed the committee members voting overwhelmingly to maintain routine postmarketing surveillance for Plan B One-Step (20 voted yes, no one voted no, and one abstained). The members appeared reassured about the safety profile of levonorgestrel EC products in the adolescent population.⁴⁸

While the committee was asked to only conduct a safety review, several members voluntarily weighed in to add their support for allowing adolescents OTC access to Plan B One-Step. The following quotes reflect the perspective of some committee members:

Dr. Jeffrey Wagener (Professor of Pediatrics, University of Colorado Medical School): “And I would add that, with only 15 serious events over 9 years, that safety in children is clearly shown. I would encourage the FDA in your future deliberations to not discriminate against children in their access to this.”

Dr. Robert Castile (Professor of Pediatrics, Ohio State University College of Medicine/Public Health): “I agree fully with my fellow pediatric pulmonologist Jeff Wagener.”

Dr. Paula Hillard (Professor of Obstetrics and Gynecology, Stanford University School of Medicine): “I think the data indicate very clearly that this product is equally safe in women of all ages, and unfortunately, the requirement that it be limited to adolescents to prescription only severely limits access to a population that desperately needs it.”

Dr. Michael White (Pediatric cardiologist, Osher Clinic Foundation in New Orleans, LA): “I would like to support the comments of Dr. Hillard.”

Dr. Lesley Walker (Professor of Pediatrics, University of Washington; Chief of division of Adolescent Medicine, Seattle Children’s Hospital): “I look forward to the day that there is no discrimination and anybody, any woman who feels she needs it of any age, can get it over the counter.”

9.4 References

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/s/

CHRISTINA Y CHANG
05/19/2012

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05/20/2012

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	21-998
Priority or Standard	Standard
Submit Date(s)	February 7, 2011
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PDUFA Goal Date	December 7, 2011
Division / Office	DNCE / ODE IV
Reviewer Name(s)	Christina Chang
Review Completion Date	October 5, 2011
Established Name	Levonorgestrel
Trade Name	Plan B One-Step
Therapeutic Class	Progestin
Applicant	Teva Women's Health, Inc.
Formulation(s)	Oral tablet
Dosing Regimen	One tablet as soon as possible
Indication(s)	Emergency contraception
Intended Population(s)	Women of reproductive potential

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

In this supplemental application, the applicant proposes to expand over-the-counter (OTC) marketing of Plan B One-Step to adolescents under age 17 years to make the product available OTC to all women of reproductive potential. The initial NDA approval for Plan B One-Step (1.5 mg levonorgestrel tablet) for use as an emergency contraceptive in July 2009 allows OTC marketing for women aged 17 years and over and prescription marketing for women younger than 17 years of age.

After reviewing the data submitted in this supplemental application, this medical officer recommends an **Approval** action for Teva's request to expand OTC marketing of Plan B One-Step to all females of reproductive age pending satisfactory negotiation of labeling.

1.2 Risk Benefit Assessment

During the Agency's review of data submitted to support over-the-counter status for Plan B (NDA 21-045, Supplement-011, 0.75 mg levonorgestrel tablet, two doses taken 12 hours apart), then Acting CDER Director Dr. Steven Galson concluded that an insufficient number of adolescents was included in the label comprehension and actual use studies conducted to support non-prescription marketing of Plan B without age restriction.¹ Specifically, Dr. Galson noted that only 76 of 656 eligible subjects in the label comprehension study were \leq 16 years old, and only 29 of 585 eligible subjects who were dispensed Plan B in the actual use study were \leq 16 years old (20 of the 29 were 16 year-olds). As a result, Dr. Galson rejected the recommendations made by a Joint Advisory Committee and the Agency's review staff to approve Plan B for all females of reproductive potential. In 2006, the OTC switch application was ultimately approved for women age 18 and older but not approved for adolescents under 18 years of age. Plan B remained a prescription drug for adolescents under 18 years of age. Thus, age became the sole factor in determining the marketing status of Plan B, with OTC marketing available to women age 18 and older. The unusual nature of the review process for the Plan B switch application and the resultant decision have been documented in the Government Accountability Office's November, 2005 report to Congress.² When Plan B One-Step was approved in 2009, FDA's scientific review concluded, in response to a federal court mandate to reexamine adolescent data, that both Plan B and Plan B One-Step should be labeled as OTC products for women 17 years of age and older.

In order to address the deficiency raised by Dr. Galson, the applicant has conducted a new label comprehension study (DR-LEV-301) and a new actual use study (DR-LEV-302) in adolescents using Plan B One-Step, which has a simpler dosing regimen than Plan B. The applicant has also discontinued the marketing of Plan B; following the approval of Plan B One-Step, Teva has been marketing Plan B One-Step exclusively. Generic versions of Plan B are also available.

My recommendation to approve this supplemental application is based on the following:

1. Unintended teen pregnancy remains a major public health issue in the U.S.

The pregnancy rate among U.S. adolescents remains high compared with other industrialized countries. In 2009, the Center for Disease Control and Prevention estimated that 740,000 pregnancies occurred in adolescents aged ≤ 17 years in 2005.³ Of these 740,000 pregnancies reported in 2005, 57% (422,000) resulted in a live birth, 27% (203,000) ended in an induced abortion, and 16% (116,000) ended in a spontaneous fetal loss. A total of 16,000 pregnancies were estimated to have occurred among adolescents under age 15 years; of these, an equal number (approximately 7000) resulted in live births and induced abortions, while 2000 ended in spontaneous fetal losses.

Adolescent pregnancies incur enormous societal costs. Short-term and long-term adverse health consequences of teen pregnancy have been documented for both the mother and child.⁴ Adverse economic consequences have also been documented for teen mothers and for their children. Adolescent mothers have lower educational attainment and are more likely to be affected by poverty. The National Campaign estimated in 2006 that teen childbearing costs taxpayers at least \$9.1 billion annually.⁵

Despite the fact that the majority of adolescent pregnancies resulted in live births, evidence shows that a large proportion of these pregnancies were unintended. Findings of an analysis by Finer et al. indicate that 100% of the pregnancies in those younger than 15 had been unintended, compared to 87% of pregnancies in 15- to 17-year-olds (based on 2001 data).⁶ Finer et al. also showed that abortion rate correlated with the “intendedness” of pregnancies. Specifically, 51% of the pregnancies occurring in adolescents younger than 15 years ended in induced abortion, whereas 39% of unintended pregnancies occurring in those aged 15 to 17 years ended in abortion. Preventing unintended pregnancies from occurring can decrease the number of abortions in adolescents.

Therefore, I believe that a public health problem of this magnitude should be addressed with all armamentaria available, including increased access to emergency contraception for those who choose to use it.

2. Emergency contraception has a limited therapeutic window.

The small therapeutic window of levonorgestrel when used as an emergency contraceptive (EC) makes timely access to this product essential. Although the approved labeling for levonorgestrel EC recommends that the product be taken within 72 hours of unprotected intercourse, it is important to note that the EC efficacy is inversely related to elapsed time following unprotected intercourse. Data supporting the Plan B marketing application showed that earlier use of EC increases efficacy. The multi-national study sponsored by the World Health Organization (WHO)⁷ found a pregnancy rate of 0.4% if levonorgestrel is taken within 24 hours following unprotected intercourse, compared to pregnancy rates of 1.2% and 2.7% if levonorgestrel is taken in the 25-48 hour and 49-72

hour windows, respectively. Clearly, for women who have had unprotected sex, access to EC within 24 hours of coitus offers the greatest likelihood to avoid unintended pregnancy. OTC, rather than Rx availability is more likely to allow earlier use of EC in this limited window.

That having been said, the current reality is that when an adolescent finds herself in need of EC, she is likely to face significant logistical and financial barriers in obtaining EC. Specifically, she would need to identify a healthcare provider, secure an appointment with this provider, obtain the prescription for EC, and purchase the product from a pharmacy that has it in stock, all within 72 hours. Although the practice guideline issued by the American College of Obstetricians and Gynecologists does not require a clinical examination prior to provision of EC,⁸ the reality is that few providers would prescribe EC for an adolescent whom they have not previously seen in the office as a patient. In the opinion of this medical officer, the potential risk of unintended pregnancy or subsequent pregnancy termination resulting from delayed access to EC carries a far greater clinical significance for the adolescents than their possible misuse of a single dose of levonorgestrel EC.

3. There is no unique safety concern for levonorgestrel emergency contraception in adolescents.

Levonorgestrel as an active ingredient has a decades-long safety record. Since the prescription (Rx) approval of Plan B in 1999, a favorable safety profile of levonorgestrel used as EC has also been shown. The mechanism of action of levonorgestrel EC in post-menarcheal females is the same, regardless of age. The side effect profile of levonorgestrel EC is not distinguishable based on age of the user alone. Indeed, my review has not identified unique safety signals for levonorgestrel EC specifically in adolescents (compared with adults).

4. Results of DR-LEV-302 and DR-LEV-301 satisfactorily demonstrate that adolescents aged 13 to 17 years can understand the product label and use Plan B One-Step safely and appropriately.

As discussed under section 5.3.1 of this review, results of DR-LEV-301 have demonstrated successful comprehension of key elements of the label by adolescents. Also, as discussed in detail under section 5.3.2.4 of this review (under medical officer comment), results of DR-LEV-302 have demonstrated that 99% of the adolescent subjects were able to correctly self-select to take Plan B One-Step, and that 92.3% of subjects were able to use the product correctly. In addition, these adolescent subjects performed favorably with respect to correct product usage when compared to adult subjects who participated in the actual use study for Plan B. With respect to label comprehension study data, results of DR-LEV-301 also compared favorably with the label comprehension study conducted to support the Plan B OTC switch application; the reader is referred to section 5.3.1 for results of DR-LEV-301 and section 9.1 Literature Review (Raymond et al. 2002) for additional details. For one communication objective in the Plan B One-Step label in particular, the adolescents in DR-LEV-301 demonstrated

superior understanding in comparison with adult subjects. While 92.2% of DR-LEV-301 subjects understood that Plan B One-Step should not be used for regular contraception, 67% of the mostly adult subjects in the Plan B label comprehension study understood that Plan B should not be used for regular contraception. Thus, data submitted in this supplemental application have satisfactorily mitigated the concerns raised by Dr. Galson previously. OTC marketing of Plan B One-Step should be available to the adolescent population.

5. OTC switch for levonorgestrel EC without age restriction was overwhelmingly endorsed by the 2003 joint session of the Nonprescription Drug Advisory Committee (NDAC) and the Advisory Committee for Reproductive Health Drugs (ACRHD).
Of the 27 members who cast votes on whether marketing status for Plan B should be switched to OTC, 23 voted yes while four voted no. Members of the joint Advisory Committee reached their decision after considering efficacy and safety data of Plan B, as well as results from the label comprehension study and actual use study provided in NDA 21-045/S-011. Having weighed the benefit of EC against the risk of misuse, the majority of the panel supported the switch **without age restriction**. I concur with the panel's recommendation. The reader is referred to detailed discussion and summary of the Committee's deliberation under section 9.3 Advisory Committee Meeting.
6. Availability of EC has not been shown to adversely affect the contraceptive behavior.
To date, clinical trials have been consistent in demonstrating a lack of association between advance provision of EC and adverse reproductive health outcomes subsequently (with follow-up up to 12 months).⁹⁻¹⁴ Specifically, advance provision of EC has not been shown to increase the incidence of sexually transmitted diseases, decrease condom use, encourage adoption of less reliable contraceptive methods, or otherwise negatively affect sexual and reproductive behavior. While I am sensitive to the concerns for the potential of adolescents engaging in more risky behavior, available scientific data to date have consistently allayed such concerns. Consequently, I do not believe these concerns should eclipse the efforts to ensure that all adolescents have enhanced access to EC when and if they choose to use it. In addition, considering the side effects of repeated use (irregular bleeding), the package configuration (each package contains only a single tablet), and potentially prohibitive cost (one package of Plan B One-Step is currently priced similarly as a course of an entire month-worth of oral contraceptive pills), I believe it is unlikely for sexually active adolescents to resort to EC as their long-term, routine contraceptive.
7. Having the same labeling for contraceptive products for all females of reproductive age is consistent with the Agency's past regulatory paradigm
It should be noted that FDA's findings for efficacy and safety of Plan B One-Step did not specify a lower-bound age limit. Furthermore, not stating a lower age limit in the target population is consistent with FDA's past decisions on contraceptive drug products (hormonal contraceptives and spermicide) and barrier device methods (condoms and diaphragm). These decisions were based the understanding that reproductive physiology,

rather than chronological age, determines the need for contraception. The applicant seeks no lower age limit for OTC access to Plan B One-Step. I concur that no lower age limit is necessary because Plan B One-Step is safe and effective for all females of reproductive age, and the age at which reproductive ability occurs is variable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None; as per the law, postmarketing Risk Evaluation and Mitigation Strategies are not applicable to OTC products. Further, the CARE program, implemented in 2006 to monitor adherence to the age limit at point of purchase for Plan B and voluntarily extended by the applicant for Plan B One-Step in 2009, would become obsolete if this supplemental application becomes approved.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

OTC marketing of Plan B One-Step (1.5 mg levonorgestrel tablet) for use as an emergency contraceptive is already approved for women aged 17 years and over. The efficacy and safety of Plan B One-Step as an emergency contraceptive is already well-established. In this supplemental application, the applicant proposes to expand OTC marketing to adolescents under age 17 years to make the product available to all women of reproductive potential.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1. Approved treatments for emergency contraception

Propriety (pharmacological) name	Formulation	Approval mechanism	Marketing status
Plan B and its generics (levonorgestrel 0.75 mg)	Tablet	NDA 21-045, ANDAs 78-665/90-740	OTC for 17 and older; Rx for 16 and under
Ella (ulipristal acetate 30 mg)	Tablet	NDA 22-474	Rx
Preven Emergency Contraception Kit (ethinyl estradiol 0.05 mg/levonorgestrel 0.25 mg)	Tablet	NDA 20-946	Rx (no longer marketed for business reasons)

Of note, a frequently used regimen utilizes combination oral contraceptive pills taken as a two-dose, 12-hour regimen; each dose contains 100 mg ethinyl estradiol and 0.5 mg levonorgestrel (the Yuzpe regimen).⁸

2.3 Availability of Proposed Active Ingredient in the United States

The active moiety in Plan B One-Step, levonorgestrel, is a second-generation progestin with an established record of safe use; it has been used in prescription (Rx) contraceptive products for over four decades. Levonorgestrel is the progestin component in combination oral contraceptives with daily dosages ranging from 0.05 mg to 0.15 mg. In contrast with the European market, where progestin-only oral contraceptives containing levonorgestrel at a daily dose of 0.03 mg have been marketed for more than three decades, there are no approved oral contraceptive formulations containing single-ingredient levonorgestrel in the U.S.

Levonorgestrel is also found as a single ingredient in FDA-approved contraceptive implants (Norplant, Norplant II) and an intrauterine device (Mirena). Finally, levonorgestrel is also FDA-approved in a two-dose regimen (0.75 mg per dose, for the same cumulative dose of 1.5 mg) for emergency contraception as Plan B and three generic products. Table 2 presents approved products other than Plan B One-Step containing levonorgestrel.

Table 2. Available therapies other than Plan B One-Step which contain levonorgestrel

Therapeutic class	Examples	Marketing status
Combination oral contraceptives	Enpresse-28, Seasonale	Available in and outside U.S.
Progestin-only oral contraceptives	Norgeston, Microval	Not available in U.S.
Implants	Norplant, Norplant II	No longer marketed in U.S.
Intrauterine device	Mirena	Available in and outside U.S.
Emergency contraception	Plan B and its generic versions	Available in and outside U.S.

2.4 Important Safety Issues With Consideration to Related Drugs

There is a well-established favorable safety profile for progestin-only drugs. Levonorgestrel, the active moiety in Plan B One-Step, has a wide margin of safety. In clinical trials, the most commonly reported adverse events were menstrual changes, nausea, abdominal pain, fatigue, headache, and dizziness. Considering that the use of Plan B One-Step is limited to a single dose, significant safety issues are not expected.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Plan B One-Step and the closely related product, Plan B, have had a lengthy and intertwined history, necessitating numerous interactions between the Agency and the applicant*. The following is a chronological summary of the regulatory history pertinent to Plan B One-Step:

* There have been a number of applicants for Plan B and Plan B One-Step due to acquisitions: Women's Capital Corporation, Barr Research Inc, Duramed Pharmaceuticals Inc, and Teva Women's Health Inc. For ease of reference, all are referred to as "the applicant" in this review.

- 1) August 24, 2006: Approval of Plan B set a precedent for concurrent Rx/OTC dual marketing status based on age alone, allowing OTC marketing to women aged 18 years and older but retained Rx marketing to adolescents aged 17 years and under.
 - Center Director-level reviews cited inadequate data to demonstrate that Plan B can be used safely by adolescents under 16 years of age.^{15, 16}
 - Commissioner-level decision cited concerns for point-of-purchase enforcement issues.¹⁷

The Agency's determination that such adolescent data are necessary is based on reasoning articulated by Dr. Galson (then Acting Director, Center for Drug Evaluation and Research) in his memorandum to NDA 21-045 (Plan B), dated August 26, 2005. Citing cognitive differences between adolescents and older women, and noting that few adolescents were included in the label comprehension and actual use studies conducted to support OTC switch for Plan B, Dr. Galson objected to the extrapolation of consumer study findings from older to younger women. His decision against approval overruled the recommendations for approval made by the Office of Drug Evaluation (ODE) III and then Office of Nonprescription Products (now ODE IV), and the recommendations of the 2003 Joint Advisory Committee.

- 2) November 22, 2006: Approvable action for Plan B One-Step cites the absence of OTC labeling.¹⁸ The applicant had sought Rx-only marketing of Plan B One-Step. The applicant was asked to revise Plan B One-Step labeling to be consistent with that of Plan B, reflecting dual marketing status.
- 3) May 22, 2007: meeting with the applicant to discuss studies required to support full OTC access for Plan B One-Step.¹⁹
 - A label comprehension study and an actual use study in adolescents will be required to support full OTC access for Plan B One-Step.
 - FDA provided comments on the design of these studies. Dr. Galson provided input into the study design and recommendations.
 - The applicant expressed concern over enrolling 11-year-olds for both consumer studies.
 - FDA requested information supporting the sponsor's contention that enrollment of 11-year-olds in both studies would not be feasible because females in this age group generally do not present for emergency contraception.
- 4) December 21, 2007: Advice Letter to the applicant.²⁰
 - There should be no lower age restriction for enrollment for both label comprehension study (DR-LEV-301) and the actual use study (DR-LEV-302).
 - For DR-LEV-301, a minimum of 50 subjects in each age group (12, 13, 14, 15, 16, and 17 year olds) should be enrolled.

- For DR-LEV-302, enroll a minimum of 25 subjects who are 14, 15, 16, and 17 years of age; also, enroll a minimum of 25 subjects who span the 11-13 year-old age group.
- 5) January 16, 2008: Advice Letter to the applicant:²¹
 - Provided statistical comments for DR-LEV-301.
 - 6) June 4, 2008: IND # 74,294 was opened with actual use study protocol DR-LEV-302.
 - 7) August 18, 2008: Advice Letter to the applicant provided additional statistical comments for DR-LEV-302.²²
 - 8) March 23, 2009: An order was issued by United States District Court Judge Edward Korman, directing the Agency to:²³
 - Permit the applicant to make Plan B available to women 17 and older without prescription within 30 days.
 - Reconsider whether to approve Plan B for OTC status without age or point-of-sale restriction.
 - 9) June 1, 2009: Meeting with the applicant to discuss regulatory and developmental pathway to support full OTC status for both Plan B and Plan B One-Step. The sponsor will need to:²⁴
 - Fully address concerns regarding nonprescription use of Plan B by women 16 years of age and younger that were articulated in Dr. Galson's memorandum dated August 26, 2005 and the May 6, 2004 letter.
 - A supplemental application for Plan B would not qualify for pediatric exclusivity, since the label comprehension study and actual use study were not conducted in response to the Agency's Written Request. However, it may be possible for pediatric exclusivity to be granted for the Plan B One-Step product based on the ongoing DR-LEV-302.
 - 10) April 21, 2009: Advice Letter to the applicant:²⁵
 - Citing CDER Advice Letter²⁶, DNCE determined that Plan B may be made available OTC to women 17 years of age and older.
 - 11) July 10, 2009: Approval of Plan B One-Step and labeling change for Plan B were simultaneously granted. Both products were made available OTC for women aged 17 years and older and Rx-only for adolescents aged 16 years and under.²⁷
 - 12) April 28, 2010: Meeting with applicant to discuss Proposed Pediatric Study Request (PPSR), Written Request (WR) to obtain pediatric exclusivity:²⁸
 - Under the Best Pharmaceuticals for Children Act (BPCA), FDA written requests address data needs for the active moiety (levonorgestrel), not a specific drug

product. The applicant will need to justify submitting a PPSR solely for Plan B One-Step.

- FDA determined that applicant has provided adequate information to justify removing the quota for enrollment of 11-to 13-year-olds for DR-LEV-302. An IND amendment should be submitted to formalize this change in the protocol.
- If FDA issues a WR, and the sponsor accepts the WR, then the efficacy supplement proposing to expand OTC access to adolescents younger than 17 years of age will be acceptable for priority review.

13) February 7, 2011: current submission requesting priority review.

- Review team has determined that this efficacy supplemental application does not qualify for priority review based upon the criteria listed in the Prescription Drug User Fee Act of 1992 as well as the CDER Manual of Policies and Procedures 6020.3 – Priority Review Policy.

2.6 Other Relevant Background Information

Based on the provided worldwide marketing authorization status report, the 1.5 mg levonorgestrel tablet is available as an emergency contraceptive in 69 countries. Of these, OTC marketing has been approved in 32 countries, including the United States. However, the U.S. is the only country where OTC access, when granted, can be restricted solely based on the users' age. The applicant notes that levonorgestrel 1.5 mg tablet has not been withdrawn from any markets due to safety or efficacy reasons.

In response to FDA's information request, Teva submitted U.S. distribution data since the commercial launch of Plan B One-Step following the July, 2009 dual-status marketing approval. This information was submitted as an amendment on March 31, 2011. Sources for such distribution data include prescription data from IMS, retail demand from A.C. Nielson, and distribution from Teva's internal sources. The time period covered was from July, 2009 through the end of January, 2011. The distribution data are summarized in Table 3.

It should be noted that the number of units distributed to non-profit entities (such as Planned Parenthood) was listed separately under "Clinic Distribution." Teva acknowledged that there was no mechanism of tracking when and how the product was provided (i.e., whether a prescription had been written, or whether it had been dispensed or remained in the clinic) once the products were received by these non-profit entities.

While the total number units filled by prescription can be documented, Teva states that the IMS database does not capture the age of the person filling the prescription. The numbers provided represent the maximum possible units sold by prescription to women age 16 and younger.

Table 3. U.S. Distribution information for Plan B and Plan B One-Step, July 2009 through January 2011 (taken from the March 31, 2011 amendment to NDA 21-998/S-02, Cover Letter)

Month	Plan B			Plan B One-Step		
	OTC Sales	Rx Filled	Clinic Distribution	OTC Sales	Rx Filled	Clinic Distribution
9-Jul						(b) (4)
9-Aug						
9-Sep						
9-Oct						
9-Nov						
9-Dec						
10-Jan						
10-Feb						
10-Mar						
10-Apr						
10-May						
10-Jun						
10-Jul						
10-Aug						
10-Sep						
10-Oct						
10-Nov						
10-Dec						
11-Jan						
Total						

For the covered period, a total of (b) (4) units of Plan B were distributed by Teva. Excluding the non-profit clinics, (b) (4) units were distributed commercially. Of the commercial units sold, prescriptions to women aged 16 and under accounted for 19.5%. For Plan B One-Step, a total of (b) (4) units were distributed by Teva; commercial distribution accounted for (b) (4) units, or 71%. Prescriptions to women aged 16 and younger accounted for 6.4% of the commercially distributed units.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, this application presents data in an acceptable fashion to facilitate the review process. While the initial submission did not include information and analysis from safety databases such as FDA’s Adverse Events Reporting System (AERS) and the World Health Organization (WHO)’s International Drug Monitoring Program, the applicant responded to the Agency’s Information Request within the expected time frame to ensure completeness of the final submission. In addition, although the original submission included raw datasets which were not analyzable, the correct, analysis dataset was provided in a timely fashion by the applicant.

Despite the timely follow-up to Agency's Information Requests, however, analyses provided by the applicant were superficial in that they lacked clinically meaningful interpretations. This flaw in the submission was addressed by independent analyses of submitted data conducted by this medical officer. Refer to section 5.3.2.4 Analysis of Primary Endpoints for details.

Only one clinical study (actual use study, DR-LEV-302) is submitted in this supplemental application. The applicant did not convene a central Investigators' Meeting for this study; staff at each site were trained separately by the applicant according to a standardized training curriculum.

In a Quality Assurance Statement dated February 2, 2011, the applicant stated that no audits had been performed by Teva. Among the five sites participating in this study, enrollment at University of California, San Francisco General Hospital (hereafter UCSF) significantly outnumbered other sites, because UCSF was the sole study site during the study period when Plan B One-Step remained an investigational product. Specifically, the UCSF screened 346 subjects (91.3% of 379 total screened) and enrolled 316 subjects (92.1% of 343 total enrolled) in DR-LEV-302. Therefore, the Division of Nonprescription Clinical Evaluation (DNCE) sent a consult to the Division of Scientific Integrity (DSI) pertaining to the inspection of the UCSF site for this study. The inspection was conducted in July 2011. The DSI report, finalized on September 23, 2011, concluded that data submitted in support of this supplemental application appear reliable.

3.2 Compliance with Good Clinical Practices

The applicant stipulates that study DR-LEV-302 was conducted according to the laws, regulations, and administrative provisions relating to the implementation of Good Clinical Practice (GCP) in the conduct of clinical trials on medical products for human use, as applicable by the U.S. 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, and 312, and in accordance with the Declaration of Helsinki and its updates. The study protocol and all subsequent amendments were reviewed and approved by the respective Institutional Review Board (IRB) at each study site.

3.3 Financial Disclosures

The applicant certified that there were no financial conflicts of interest for any principal investigators and sub-investigators who participated in the conduct of DR-LEV-302, the sole clinical study submitted in support of this application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

The study product, Plan B One-Step, is already an approved product subject to this NDA. The study drug is supplied to Teva Women's Health, Inc. by Gedeon Richter Ltd. (Budapest,

Hungary), the same manufacturer for approved Plan B and Plan B One-Step products. Therefore, there are no issues pertinent to chemistry, clinical microbiology, pharmacology/toxicology, or clinical pharmacology.

4.1 Chemistry Manufacturing and Controls

Not applicable.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Not applicable.

4.4 Clinical Pharmacology

Not applicable.

5 Sources of Clinical Data

The primary source of clinical data is the open-label, non-comparative actual use study, DR-LEV-302. The other consumer study submitted to support this application, DR-LEV-301, is a label comprehension study where no subjects were administered any study product.

There are no efficacy data submitted in this supplemental application. Additional information provided by the applicant is comprised of postmarketing safety data from the following databases:

- Teva's own postmarketing experience
- FDA's Adverse Event Reporting System (AERS)
- World Health Organization's (WHO) International Drug Monitoring Program

Finally, the applicant provided a literature review to identify publications pertinent to the understanding and use of emergency contraception in the adolescent population.

5.1 Tables of Studies/Clinical Trials

Table 4. Studies submitted in this application

Study	Design	Subjects
DR-LEV-301, label comprehension study	Survey	Females age up to 17 years, able to read and understand English
DR-LEV-302, actual use study	Single-arm, open-label study in simulated OTC setting	Females age 1-17 years, needing emergency contraceptive for current and personal use

5.2 Review Strategy

DNCE is the division charged with the primary responsibility for reviewing this application. The label comprehension study (DR-LEV-301) is reviewed by DNCE's social science analyst, Murewa Oguntimein. This medical officer is responsible for reviewing the actual use study (DR-LEV-302), postmarketing safety data, and pertinent literature. The statistical review team will provide input on data analysis for both DR-LEV-301 and DR-LEV-302.

5.3 Discussion of Individual Studies/Clinical Trials

In response to FDA's request to provide data to demonstrate that Plan B can be used safely and appropriately by adolescents, the applicant conducted DR-LEV-301 and DR-LEV-302 to support the removal of age restriction at the point of purchase for OTC use.

5.3.1 DR-LEV-301 (Label Comprehension Study)

DR-LEV-301 is a multicenter (14 sites in 8 U.S. cities) survey. Results of this study were submitted under IND 74,294 (June 3, 2008) and subsequently published in 2009.²⁹ The objective is to estimate the proportion of adolescents aged 12 to 17 years who would demonstrate an understanding of the six Key Concepts from reviewing the Plan B One-Step package and completing the study questionnaire. A brief summary of findings from DR-LEV-301 is presented here in this medical officer's review; the reader is referred to DNCE's social scientist review for additional detail.

The six Key Concepts tested for comprehension were the following:

Primary concepts:

- Plan B One-Step is indicated for prevention of pregnancy after unprotected sex.
- Plan B One-Step should be taken as soon as possible after sex.
- Plan B One-Step does not prevent sexually transmitted diseases or HIV/AIDS.

Secondary concepts:

- Plan B One-Step should not be used in place of regular contraception.
- Plan B One-Step should be taken within 72 hours after sex.

- Plan B One-Step should not be used by women who are already pregnant.

Between October 22, 2007 and February 22, 2008, 377 subjects were interviewed. Of these, 335 (89%) were eligible for enrollment. Of the eligible subjects, 327 (98%) completed the survey. Enrollment by age of the 335 subjects was well distributed among all ages from 12 to 17 years; this is presented in Table 5 below.

Table 5. Number of subjects enrolled by age and by study site in DR-LEV-301

	Atlanta, GA	Denver, CO	Los Angeles, CA	Philadelphia, PA	St. Louis, MO	Seattle, WA	Total
Age							
12	10	6	15	4	12	7	54
13	11	8	15	6	10	6	56
14	9	8	10	8	11	8	54
15	8	9	12	11	8	11	59
16	9	10	8	18	7	5	57
17	8	12	9	9	8	9	55

The six Key Concepts were each understood by 83 – 96% of subjects, as summarized in Table 6 below.

Table 6. Number and proportion of subjects by age demonstrating understanding of the label

	Key Concepts	Subjects demonstrating understanding N (%)		Total N = 335 (100%)
		12 to 14 year-olds N = 164	15 to 17 year-olds N = 171	
1	Plan B One-Step is indicated for prevention of pregnancy after unprotected sex	139 (85%)	161 (94%)	300 (89.6%)
2	Plan B One-Step should be taken as soon as possible after sex	130 (79%)	147 (86%)	277 (82.7%)
3	Plan One-Step does not prevent sexually transmitted disease or HIV/AIDS	145 (88%)	165 (96%)	310 (92.5%)
4	Plan B One-Step should not be used in place of regular contraception	148 (90%)	161 (94%)	309 (92.2%)
5	Plan B One-Step should be taken within 72 hours after sex	151 (92%)	168 (98%)	319 (95.2%)
6	Plan B One-Step should not be used by women who are already pregnant	153 (93%)	167 (98%)	320 (95.5%)

*Trade name used in the questionnaire was Plan B 1.5, the proposed trade name for Plan B One-Step at the time when DR-LEV-301 was conducted.

Medical officer comment:

As per Agency's request, DR-LEV-301 enrolled more than 50 adolescent subjects for each age. The enrolled population was also racially and ethnically diverse, with approximately one-fourth of subjects self-identifying as African American, and approximately one-fifth as being of Hispanic descent (26.3% and 20.6%, respectively). In addition, 140 subjects (41.8%) scored at a 7th grade level or lower on the Rapid Estimate of Adult Literacy in Medicine-Teen (REALM-Teen) assessment; the number of lower literacy subjects enrolled exceeded by 100% the minimum number of lower-literacy subjects planned. Lastly, the study population was predominantly naïve with respect to prior experience with emergency contraception. Specifically, only 7.2% of subjects had previously used emergency contraception, much fewer than 25% permitted by the protocol.

Although acceptable target comprehension rates were not pre-specified, these adolescent subjects appeared to have understood well Key Concept #5, recognizing that the product should be taken within 72 hours following unprotected intercourse. This finding is reassuring because this is the concept most pertinent to ensuring product efficacy. The finding that the more abstract nature of Key Concept #2 appeared to be somewhat less understood is less important, because the subjects demonstrated excellent comprehension of Key Concept #5.

Based on summary results from DR-LEV-301, adolescents in both age groups appear to have demonstrated very good understanding for key elements in the Plan B One-Step label. I believe the level of comprehension exhibited by these adolescent subjects is sufficient to address the concerns expressed in Dr. Galson's 2005 memorandum. The reader is referred to DNCE social science review for additional, detailed discussion.

5.3.2 DR-LEV-302 (Actual Use Study)

DR-LEV-302 is a non-comparative, open-label, single-use, multicenter case series study to assess the ability of females 11 to 17 years of age to appropriately self-select and correctly use Plan B One-Step. The primary objectives of this study were to determine 1) whether adolescent subjects can appropriately self-select to take Plan B One-Step, and 2) after having been dispensed the product, whether adolescent subjects can correctly use Plan B One-Step based on directions in the label.

5.3.2.1 Study Design and Conduct

The setting of this study simulates the OTC environment because the subjects, having self-identified a need for emergency contraception (EC), presented to the study sites requesting EC, and obtained Plan B One-Step for personal use without provider direction. To avoid introducing bias and to ensure integrity of the study, the study staff utilized the IRB-approved Screening/Enrollment Script to strictly control the information subjects were given about the study and the study product, Plan B One-Step. After reading the product information on the front

and back panels of the study package, the subjects had to make their own determination about whether to receive and use Plan B One-Step (without any additional assistance and guidance from study staff or a healthcare provider). The subjects alone assessed whether to take Plan B One-Step, when to take it, and potential risks and side effects of this product.

Conduct of the study follows the process below:

Subjects who were interested in screening for the study were asked to complete a self-administered IRB-approved Screening Questionnaire to record reason(s) for visiting the clinic, whether they were requesting EC for themselves or someone else, whether they were requesting EC for current or future use, and to assess eligibility. This Screening Questionnaire collected demographic information and assessed inclusion criteria # 1 to 7:

1. Female **and** 11 – 16 years of age, inclusive;
2. Subject must be requesting EC for her own use (not for use by another person) **and** for current (not future) use;
3. Subject has not previously participated in any studies involving Plan B One-Step;
4. Subject can read and understand English, according to her own judgment;
5. Subject is willing to complete Study Questionnaires and to be contacted or return to the study site for follow-up at about one, four, and eight weeks following receipt of study product;
6. Subject is willing to read/sign the Informed Consent after the nature of the study is explained and questions about the study are answered;
7. Subject is willing to determine if she wants the study product after reading the label text on the outside of the study package, and without provider counseling.

Eligible subjects meeting all seven inclusion criteria were provided information regarding participation in the study and the IRB-approved Informed Consent Form to read and sign.

Following written informed consent, the subject was considered enrolled and given an empty, sealed OTC package of Plan B One-Step to review without additional guidance and counseling. The subject was then asked to complete a self-administered Participation Questionnaire to indicate her reasons(s) for requesting EC. This Participation Questionnaire aimed to obtain the following information:

- Sexual history and contraceptive methods previously used;
- Age at menarche;
- Allergies to medications;
- Obstetrical history and results of any pregnancy tests performed by subject or clinic staff;
- Whether she has received/used EC in the past.

In addition, she was asked to indicate whether she wanted to receive the study product. If she indicated “no,” she would record her reason(s) for choosing not to use the study product. This step is intended to assess potential subjects’ ability to appropriate self-select for taking the product.

Study staff would review the subject's self-administered Participation Questionnaire to determine if she had appropriately self-selected to receive the study product, Plan B One-Step. Plan B One-Step would only be dispensed to those subjects who appropriately self-selected **and** chose to use the study product without provider counseling.

According to the protocol, subjects who inappropriately self-selected would not be dispensed the study product; instead, these subjects would be referred to clinic staff for further assessment and treatment. Subjects who inappropriately self-selected were those indicating that they want to use the study product **and** also indicating on the Participant Questionnaire that they:

- Want to use the product for a reason Plan B One-Step is not indicated (e.g., terminate an existing pregnancy);
- Have an allergy to levonorgestrel, or
- Have positive pregnancy test(s), or
- Check "yes" to the question "Are you already pregnant?"

For the subjects who chose to use the study product **and** demonstrated appropriate self-selection, the study staff then arranged for follow-up contacts at one-, four-, and eight-week time points. Information regarding the use of study product and adverse events would be collected during these contacts.

The study design and processes outlined above are presented in tabular format in Table 7 and in Figure 1 diagrammatically.

Table 7. Study design and schedule of assessments

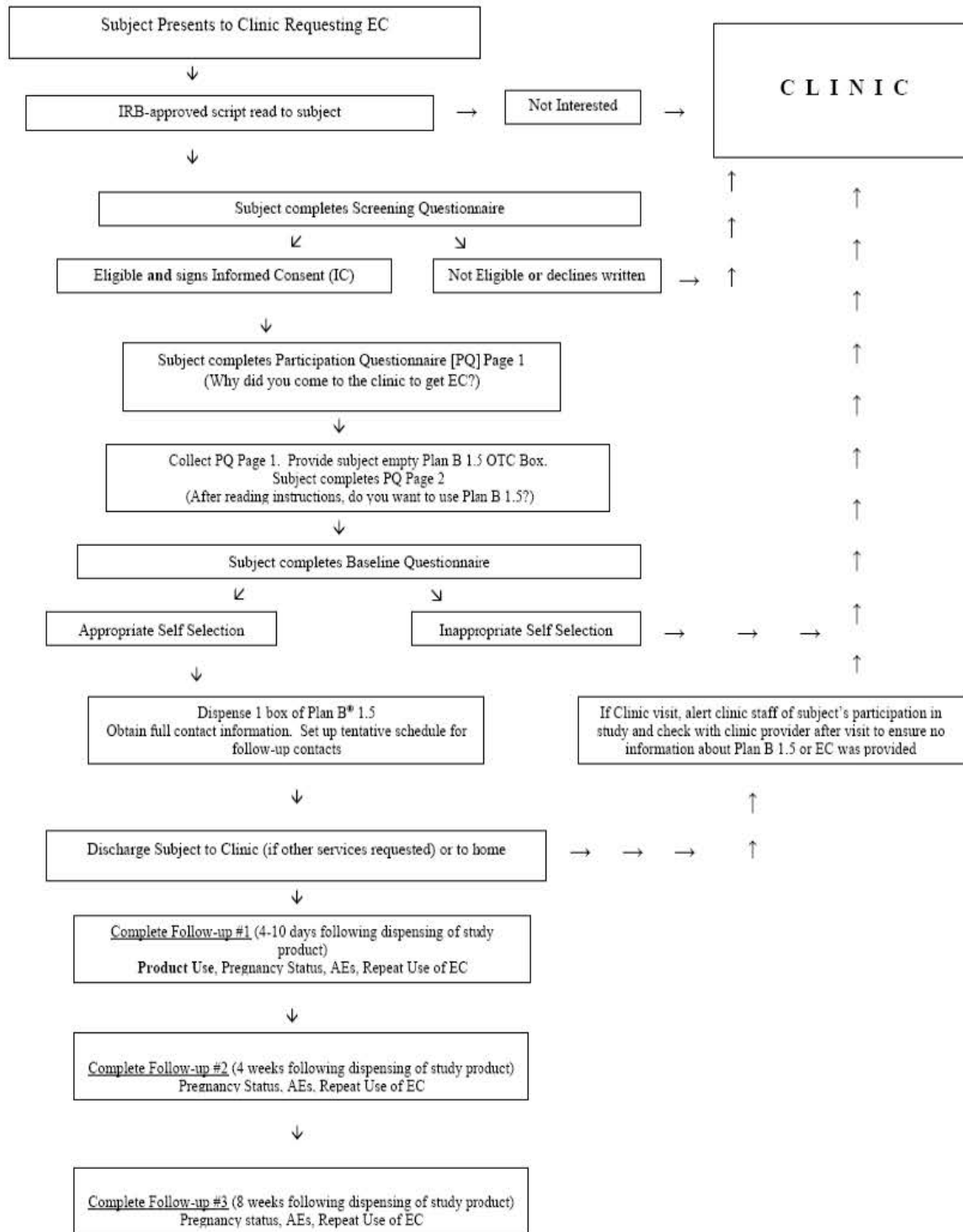
Procedure	Screening/ Enrollment	Week 1 ^a	Week 4 ^a	Week 8 ^a	Weekly thereafter (if necessary) ^b
Screening for eligibility (completion of the Self-administered Screening Questionnaire)	X				
Written informed consent	X				
Collection of baseline information (completion of Self-administered Participant and Baseline Questionnaires)	X				
Provision of Study Product (only to subjects who appropriately self-select and choose to use study product)	X				
Collection of information about use of product (completion of Follow-up Contact Questionnaire)		X			
Collection of information about adverse events and pregnancies (completion of Follow-up Contact Questionnaire)		X	X	X	X
Collection of information about subsequent EC use, such as Plan B [®] /Plan B One-Step [®] (completion of Follow-up Contact Questionnaire)		X	X	X	
Request return of unused Study Product	X ^c	X ^c			

^aFollow-up Contact was to be conducted by telephone or return clinic visit, at the discretion of the subject and study site; in addition to the one-, four-, and eight-week contacts, study sites were to conduct additional contacts if deemed necessary for the individual subject.

^bIf pregnancy status or the status of any adverse event was not clear at the time of the eight-week contact, additional contacts were to be made at weekly intervals until pregnancy status became clear and/or until all adverse events had resolved or stabilized.

^cSubjects who were dispensed study product and subsequently found to have a positive pregnancy test during the clinic portion of their visit were expected to return study product prior to leaving the clinic. Subjects who had not used the study product Plan B[®] 1.5 by the time of the one-week Follow-up contact were requested to return it to the study site using a pre-addressed mailer provided by the study site.

Figure 1. Study flow diagram



5.3.2.2 Demographics

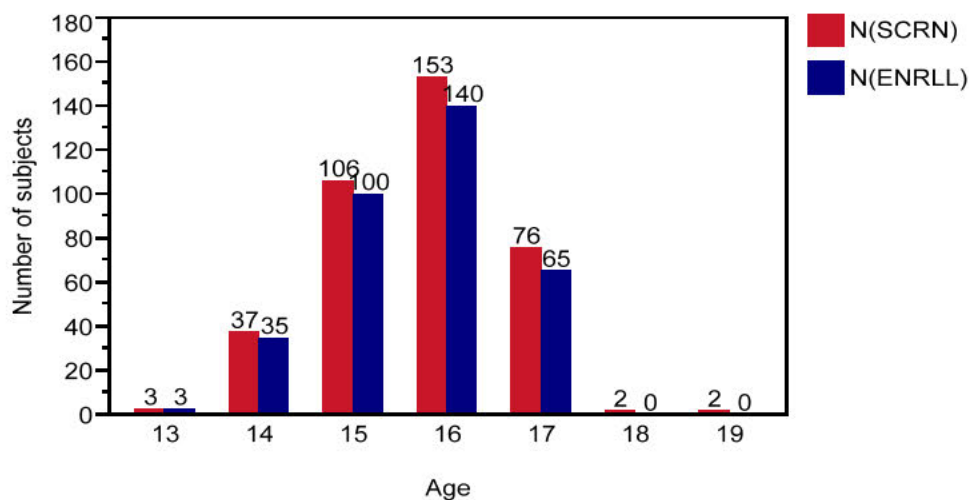
Five study sites participated in DR-LEV-302. These sites and their respective principal investigators are listed in Table 8 below.

Table 8. Clinical investigation sites

Site #	Institution	Principal investigator	Enrollment
001	University of California, San Francisco	Tina Raine-Bennett	316
002	Emory University School of Medicine	Carrie Cwiak	16
003	Children's Hospitals and Clinics of Minnesota Teen Age Medical Service	David Aughey	4
004	Hospital of the University of Pennsylvania	Courtney Schreiber	6
005	Children's Hospital Pittsburgh	Gina Sucato	1

Distribution of screened and enrolled subjects by age is presented in Figure 2 below. Juxtaposition of these two populations demonstrates proportionate enrollment for all age groups.

Figure 2. Distribution by age, screened and enrolled population in DR-LEV-302



The demographics of subjects enrolling in DR-LEV-302 are presented in the sections below, further characterized by age, by investigational site, history of previous EC use, history of previous contraceptives used, and by obstetrical history.

Table 9 summarizes demographic information by age for the Enrolled Population in DR-LEV-302.

Table 9. Demographic information for the Enrolled Population by age (in years)

Characteristic	11-13 (N=3) N (%)	14 (N=35) N (%)	15 (N=100) N (%)	16 (N=140) N (%)	17 (N=65) N (%)	Total (N=343) N (%)
<i>Ethnic Latina/Hispanic</i>						
No Answer	0	1 (2.9%)	2 (2.0%)	5 (3.6%)	9 (13.8%)	17 (5.0%)
Yes	1 (33.3%)	17 (48.6%)	56 (56.0%)	66 (47.1%)	29 (44.6%)	169 (49.3%)
No	1 (33.3%)	17 (48.6%)	41 (41.0%)	66 (47.1%)	26 (40.0%)	151 (44.0%)
Don't Know	1 (33.3%)	0	1 (1.0%)	3 (2.1%)	1 (1.5%)	6 (1.7%)
<i>Race</i>						
Latina	1 (33.3%)	14 (40.0%)	51 (51.0%)	60 (42.9%)	21 (32.3%)	147 (42.9%)
African-American	0	5 (14.3%)	11 (11.0%)	26 (18.6%)	6 (9.2%)	48 (14.0%)
Multiracial	0	3 (8.6%)	7 (7.0%)	7 (5.0%)	6 (9.2%)	23 (6.7%)
White	0	5 (14.3%)	9 (9.0%)	11 (7.9%)	14 (21.5%)	39 (11.4%)
Asian/Pacific Islander	2 (66.7%)	8 (22.9%)	18 (18.0%)	27 (19.3%)	13 (20.0%)	68 (19.8%)
Native American/ Alaskan Native	0	0	1 (1.0%)	0	0	1 (0.3%)
Other	0	0	3 (3.0%)	9 (6.4%)	5 (7.7%)	17 (5.0%)

The demographics for the enrolled population by investigational site are presented in Table 10 below.

Table 10. Demographics information for the Enrolled Population by investigation site

Characteristic	Site 1 (N=316) N (%)	Site 2 (N=16) N (%)	Site 3 (N=4) N (%)	Site 4 (N=6) N (%)	Site 5 (N=1) N (%)	Total (N=343) N (%)
<i>Ethnic Latina/Hispanic</i>						
No Answer	17 (5.4%)	0	0	0	0	17 (5.0%)
Yes	168 (53.2%)	0	1 (25.0%)	0	0	169 (49.3%)
No	126 (39.9%)	15 (93.8%)	3 (75.0%)	6 (100.0%)	1 (100.0%)	151 (44.0%)
Don't Know	5 (1.6%)	1 (6.3%)	0	0	0	6 (1.7%)
<i>Race</i>						
Latina	146 (46.2%)	0	1 (25.0%)	0	0	147 (42.9%)
African-American	23 (7.3%)	16 (100.0%)	2 (50.0%)	6 (100.0%)	1 (100.0%)	48 (14.0%)
Multiracial	23 (7.3%)	0	0	0	0	23 (6.7%)
White	38 (12.0%)	0	1 (25.0%)	0	0	39 (11.4%)
Asian/Pacific Islander	68 (21.5%)	0	0	0	0	68 (19.8%)
Native American/ Alaskan Native	1 (0.3%)	0	0	0	0	1 (0.3%)
Other	17 (5.4%)	0	0	0	0	17 (5.0%)
<i>Age (Years)</i>						
11-13	2 (0.6%)	0	1 (25.0%)	0	0	3 (0.9%)
14	34 (10.8%)	1 (6.3%)	0	0	0	35 (10.2%)
15	96 (30.4%)	1 (6.3%)	1 (25.0%)	2 (33.3%)	0	100 (29.2%)
16	119 (37.7%)	14 (87.5%)	2 (50.0%)	4 (66.7%)	1 (100.0%)	140 (40.8)
17	65 (20.6%)	0	0	0	0	65 (19.0)

The two largest investigation sites were UCSF and Emory University School of Medicine in Atlanta, Georgia, enrolling 316 and 16 subjects, respectively. The population enrolled at UCSF is racially diverse, and accounted for almost all the Latina, White, and Asian subjects enrolled. Given the size of enrollment at UCSF, its enrolled population essentially reflects the demographics of the entire study.

With respect to previous EC use, almost 40% of subjects overall reported having used EC previously. A correlation is seen between increasing age and history of EC use. None of the 13-year-olds had used EC previously, while 66.2% of the 17-year-olds had experience with prior EC use. The use history of EC by age and by study site is shown in Table 11 below.

Table 11. Previous emergency contraception use in enrolled population

By Age (in Years) at Screening					
11-13 (N=3) N (%)	14 (N=35) N (%)	15 (N=100) N (%)	16 (N=140) N (%)	17 (N=65) N (%)	Total (N=343) N (%)
0	4 (11.4%)	32 (32.0%)	56 (40.0%)	43 (66.2%)	135 (39.4%)
By Investigational Site					
Site 1 (N=316) N (%)	Site 2 (N=16) N (%)	Site 3 (N=4) N (%)	Site 4 (N=6) N (%)	Site 5 (N=1) N (%)	Total (N=343) N (%)
127 (40.2%)	5 (31.3%)	2 (50.0%)	0	1 (100.0%)	135 (39.4%)

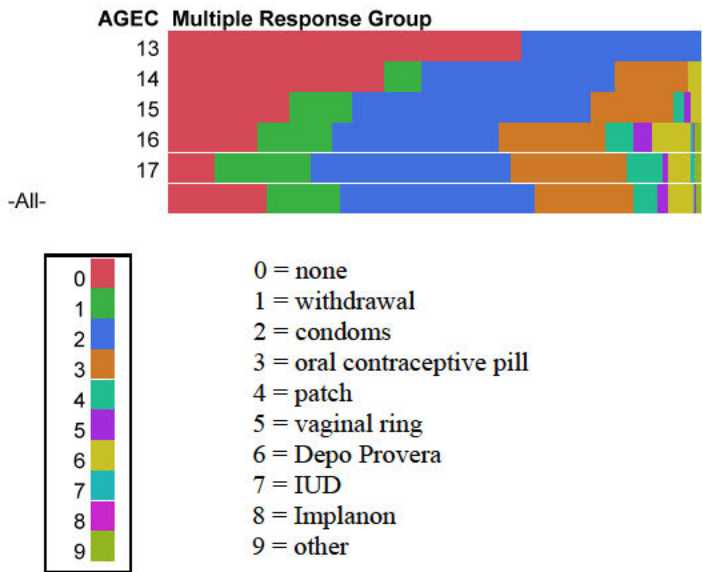
The applicant also provided the history of contraceptive method use reported by enrolled subjects; data collection allows reporting the use of more than one method. The distribution of all contraceptive methods reported by age of the subjects is shown in Table 12 and Figure 3 below.

Table 12. Contraceptive methods used by age for the Enrolled Population

Birth Control Ever Used (All Responses That Apply)	By Age (in Years) at Screening					
	11-13 (N=3) N (%)	14 (N=35) N (%)	15 (N=100) N (%)	16 (N=140) N (%)	17 (N=65) N (%)	Total (N=343) N (%)
None	2 (66.7%)	18 (51.4%)	33 (31.0%)	42 (28.6%)	12 (15.4%)	107 (29.4%)
Withdrawal	0	3 (8.6%)	17 (17.0%)	34 (24.3%)	24 (36.9%)	78 (22.7%)
Condoms	1 (33.3%)	16 (45.7%)	65 (65.0%)	77 (55.0%)	50 (76.9%)	209 (60.9%)
Pill	0	6 (17.1%)	22 (22.0%)	50 (35.7%)	29 (44.6%)	107 (31.2%)
Patch	0	0	3 (3.0%)	13 (9.3%)	9 (13.8%)	25 (7.3%)
Ring	0	0	2 (2.0%)	8 (5.7%)	1 (1.5%)	11 (3.2%)
Depo-Provera	0	1 (2.9%)	2 (2.0%)	18 (12.9%)	6 (9.2%)	27 (7.9%)
Intrauterine Device	0	0	0	1 (0.7%)	1 (1.5%)	2 (0.6%)
Implanon	0	0	0	1 (0.7%)	0	1 (0.3%)
Other	0	0	0	2 (1.4%)	1 (1.5%)	3 (0.9%)

Overall, the contraceptive methods used were primarily condoms (60.9%), oral contraceptives (31.2%), none (29.4%), and withdrawal (22.7%), in decreasing order. Importantly, use of no birth control was reported in a declining manner with increasing age, with 66.7% of 13-year-olds, followed by 51.4% of 14-year-olds, 31.0% of 15-year-olds, 28.6% of 16-year-olds, and 15.4% of 17-year-olds providing this response.

Figure 3. Contraceptive methods by age, Enrolled Population



Medical officer comment:

Condoms appear to be the preferred method of contraception in this population. Condom use has the added benefit of protection from sexually transmitted diseases. However, it is concerning that a substantial proportion (including all of the 13-year-olds and the majority of 14-year-olds) had not used any contraception and the majority across all age groups use methods that are not very effective.

In terms of obstetrical history, summary statistics are presented based on subject reports of the number of times they had been pregnant, given birth, or had abortions. These statistics are presented in Table 13 below.

Table 13. Reported obstetric history by age for Enrolled Population

History	11-13 (N=3) N (%)	14 (N=35) N (%)	15 (N=100) N (%)	16 (N=140) N (%)	17 (N=65) N (%)	Total (N=343) N (%)
<i>How Many Times Pregnant</i>						
Never	3 (100.0%)	33 (94.3%)	89 (89.0%)	125 (89.3%)	53 (81.5%)	303 (88.3%)
1 Time	0	2 (5.7%)	8 (8.0%)	14 (10.0%)	11 (16.9%)	35 (10.2%)
2 Times	0	0	2 (2.0%)	1 (0.7%)	0	3 (0.9%)
3 or More Times	0	0	0	0	1 (1.5%)	1 (0.3%)
No Answer	0	0	1 (1.0%)	0	0	1 (0.3%)
<i>How Many Times Given Birth</i>						
Never	3 (100.0%)	35 (100.0%)	93 (93.0%)	135 (96.4%)	65 (100.0%)	331 (96.5%)
1 Time	0	0	5 (5.0%)	4 (2.9%)	0	9 (2.6%)
2 Times	0	0	0	1 (0.7%)	0	1 (0.3%)
No Answer	0	0	2 (2.0%)	0	0	2 (0.6%)
<i>How Many Abortions</i>						
None	3 (100.0%)	34 (97.1%)	94 (94.0%)	130 (92.9%)	56 (86.2%)	317 (92.4%)
1	0	1 (2.9%)	3 (3.0%)	9 (6.4%)	8 (12.3%)	21 (6.1%)
2	0	0	2 (2.0%)	1 (0.7%)	1 (1.5%)	4 (1.2%)
No answer	0	0	1 (1.0%)	0	0	1 (0.3%)
<i>Pregnancy Tests in the Last 30 Days</i>						
None	3 (100.0%)	34 (97.1%)	95 (95.0%)	131 (93.6%)	60 (92.3%)	323 (94.2%)
1 or More	0	1 (2.9%)	5 (5.0%)	9 (6.4%)	5 (7.7%)	20 (5.8%)

The majority of enrolled subjects (303 subjects, 88.3% of 343) had never been pregnant prior to participating in this study. A total of 39 subjects (11.7% of 343) reported having ever been pregnant, with the majority of these (35 subjects) reporting having been pregnant once. Among the age groups, the percentage of subjects reporting they had never been pregnant was greatest for the 11 to 13- and 14-year-olds (100.0% and 94.3%, respectively), with the percentages decreasing with increasing age.

In response to the number of times the subjects had given birth, 96.5% of the subjects overall reported having never given birth. Ten subjects (2.9% of 343) reported having ever given birth. A total of 25 subjects (7.3% of 343) reported having ever had abortion. Of note, the questionnaire did not specifically ask about history of miscarriages as part of the obstetrical history.

With respect to reasons for requesting EC, the study captured the subjects' verbatim responses. The stated reasons by subject age are shown in Table 14 below. Note that each subject may give more than one reason to this inquiry.

Table 14. Reasons for requesting EC at Enrollment: Enrollment Population, by age (in years) at Screening

Question: Why Did You Come to the Clinic to Get EC Today? (All Responses That Apply)	11-13 (N=3) N (%)	14 (N=35) N (%)	15 (N=100) N (%)	16 (N=140) N (%)	17 (N=65) N (%)	Total (N=343) N (%)
Don't Want to Get Pregnant	1 (33.3%)	6 (17.1%)	39 (39.0%)	65 (46.4%)	22 (33.8%)	133 (38.8%)
Had Sex and Didn't Use a Condom/Condom Broke/Fell Off	1 (33.3%)	20 (57.1%)	53 (53.0%)	78 (55.7%)	39 (60.0%)	191 (55.7%)
Had Sex and Am Late for My Shot (or Getting Pills/Patch Refilled)	0	0	0	0	1 (1.5%)	1 (0.3%)
Had Sex and Did Not Use Birth Control Correctly	0	1 (2.9%)	0	1 (0.7%)	1 (1.5%)	3 (0.9%)
Had Sex and Don't Use Birth Control/Not Sure if Birth Control Was Used	0	12 (34.3%)	46 (46.0%)	53 (37.9%)	31 (47.7%)	142 (41.4%)
Other Correct Answer*	0	0	1 (1.0%)	5 (3.6%)	0	6 (1.7%)
Is Pregnant/Suspects is Pregnant	0	5 (14.3%)	3 (3.0%)	3 (2.1%)	5 (7.7%)	16 (4.7%)
Response Suggests Sex/Unprotected Sex >72 Hours Before requesting EC	1 (33.3%)	0	0	0	1 (1.5%)	2 (0.6%)
Takes EC Instead of Birth Control	0	0	0	1 (0.7%)	0	1 (0.3%)
Missed Period	0	0	1 (1.0%)	0	0	1 (0.3%)

Reviewer note: This table does include a legend for the asterisk (*) accompanying “other correct answer.”

Overall, the most frequently cited reasons, in descending order, were:

- The subject had sex but a condom was not used, broke or fell off (55.7% of subjects)
- The subject had sex but did not use birth control or was not sure if birth control was used (41.4% of subjects)
- The subject did not want to get pregnant (38.8% of subjects).

5.3.2.3 Subject Disposition

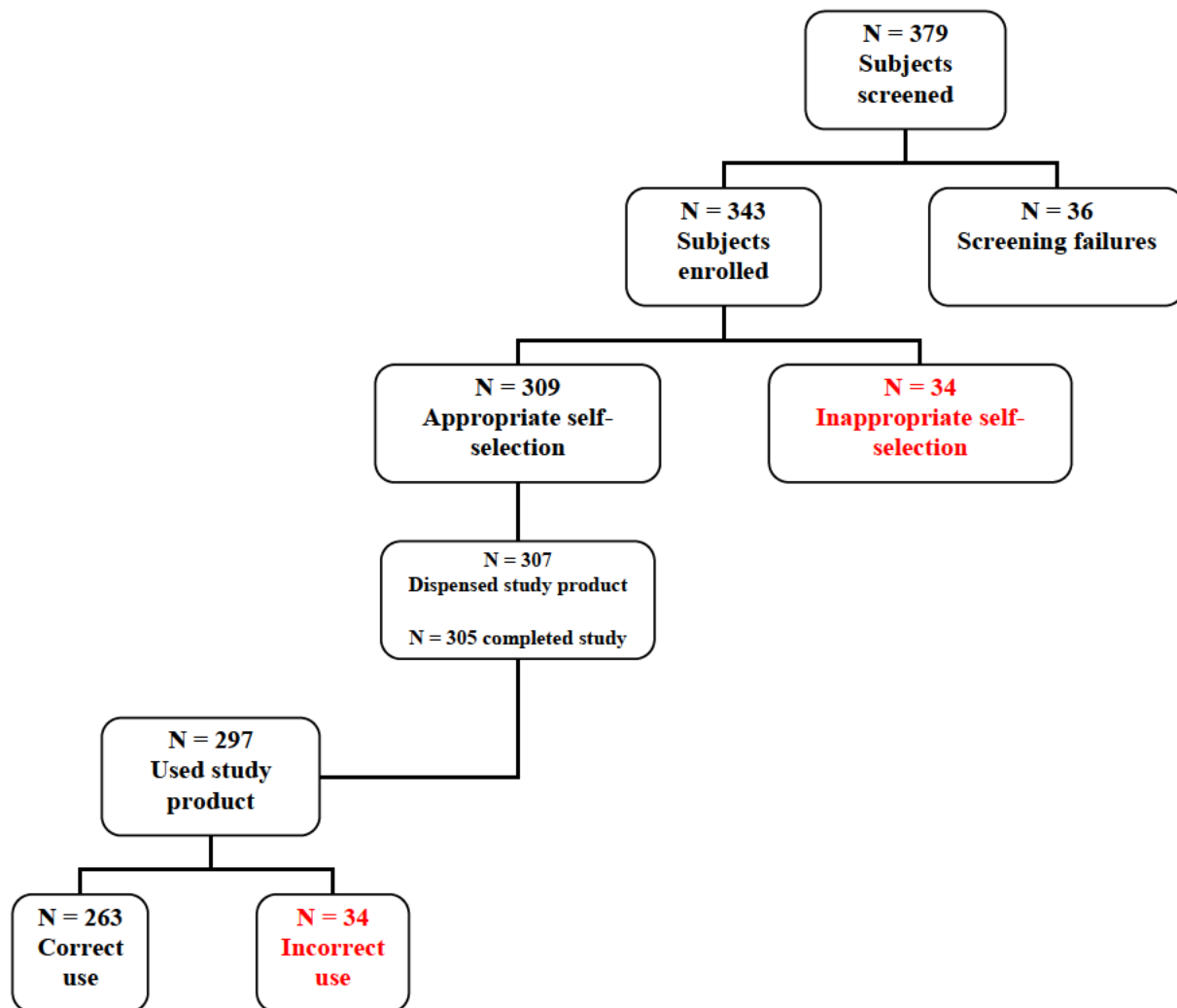
A total of 379 women were screened for the study and constitute the Screened Population representing the maximum number of subjects who were seen at the participating clinics. A total of 343 subjects, or 90.5% of those screened, met enrollment criteria. Of the 343 enrolled subjects, 309 or 90.1% demonstrated appropriate self-selection per the protocol. Of the 309 subjects who correctly self-selected, two (subjects #10086 and #10338) chose not to use the study product after reading the product label; they were not dispensed Plan B One-Step.

Therefore, 307 subjects who appropriately self-selected **and** chose to use Plan B One-Step constitute the Treated Population.

At the one-week follow-up, 297 subjects (96.7% of 307) reported having used the study product after the clinic visit. Of these, 263 subjects (88.6% of 297) used it correctly according to the protocol (i.e., within 72 hours after unprotected intercourse and following up within 10 days).

Disposition of the subjects is presented in Figure 4 below.

Figure 4. Disposition of study subjects, based on the applicant's analysis



Of the 307 subjects who were dispensed the product, 305 completed follow-up contact #1. Of these, 294 completed follow-up contact #2; 285 subjects completed all three follow-up contacts.

In response to FDA's information request, the applicant clarified the status of 12 subjects (those who were dispensed the products but had not completed all three follow-up contacts by the time the study report was finalized) via an amendment submitted on June 3, 2011. Ten of these 12 subjects finished the study by completing all three follow-up contacts; two were lost to follow-up. All 10 subjects who did follow-up had reported taking the study product and this information was already available at the time the study report was finalized. None of the ten subjects reported any adverse events. The applicant maintains that no changes to the results and study conclusions are warranted based on this update.

Medical officer comment:

Notwithstanding the applicant's assertion that findings from these 12 subjects would not change the study conclusion, I performed a sensitivity analysis to assess outcome based on the intent-to-treat cohort. See further discussion pertaining to actual use in section 5.3.2.4 Analysis of Primary Endpoints.

5.3.2.4 Analysis of Primary Endpoints

Since the efficacy of the single-dose regimen of levonorgestrel 1.5 mg is well established, DR-LEV-302 did not employ any traditional efficacy measures. Rather, the endpoints utilized in DR-LEV-302 are intended to address standard requirements of an Rx-to-OTC switch process, which requires evaluation of potential consumers' ability to 1) **self-diagnose** the condition and that treatment with the product is appropriate for them, and 2) **self-treat** with the product according to the product instructions, and 3) **self-manage** following use.

Two measures were considered as co-primary in nature, although one was actually a conditional outcome based on the other. The first measure was a determination of the percentage of subjects who appropriately self-selected Plan B One-Step at the Screening/Enrollment Visit after reading the product label. The second measure was the calculated proportion of subjects who, after appropriately self-selecting and being dispensed Plan B One-Step under simulated OTC conditions, correctly used the product according to the product label.

Self-selection

Appropriateness of subjects' decision-making pertaining to the use of Plan B One-Step was assessed by following the algorithm presented in Table 15 below.

Table 15. Assessment of the self-selection decision

<p>APPROPRIATE SELF-SELECTION: SUBJECT'S VERBATIM RESPONSE TO QUESTION ON PARTICIPATION QUESTIONNAIRE (Part 1) "Why did you come to the clinic today to get EC?" included at least one of the following reasons listed in 1-6 and none of the responses listed in 7-11, below.</p>
(1) I want to keep from getting pregnant (or having a baby) / I don't want to get pregnant
(2) I had sex and didn't use a condom/condom broke / not sure if used a condom
(3) I had sex and I am late for my shot (or getting my pills/patch/birth control refilled)
(4) I had sex and I used my birth control incorrectly (i.e. missed pills, patch came off)
(5) I had sex and I didn't use any birth control / not sure if I used birth control (whether or not they mention anything about pregnancy)
(6) Other "appropriate" reason, specify: _____
<p>INAPPROPRIATE SELF-SELECTION: SUBJECT'S VERBATIM RESPONSE TO QUESTION ON PARTICIPATION QUESTIONNAIRE (Part 1) "Why did you come to the clinic today to get EC?" included any one of the following reasons in 7-11 below.</p>
(7) "I am pregnant"/"think I am pregnant"
(8) "I want to prevent STIs/STDs"
(9) Subject requests EC and indicates a sex act or unprotected sex act that occurred more than 72 hours prior to the day/time she is requesting the EC
(10) "I take EC instead of birth control"
(11) Other "Inappropriate" reason, specify: _____

Overall, the applicant reported that 90.1% of enrolled subjects (309 out of 343) between the ages of 11 and 17 years demonstrated appropriate self-selection per the protocol. The lower bound of the 95% confidence interval for the proportion demonstrating appropriate decision was 86.4%. The distribution of self-selection decisions by age is shown in Figure 5 and Table 16 below.

Figure 5. Self-selection decision by age (primary objective #1): of 343 enrolled subjects

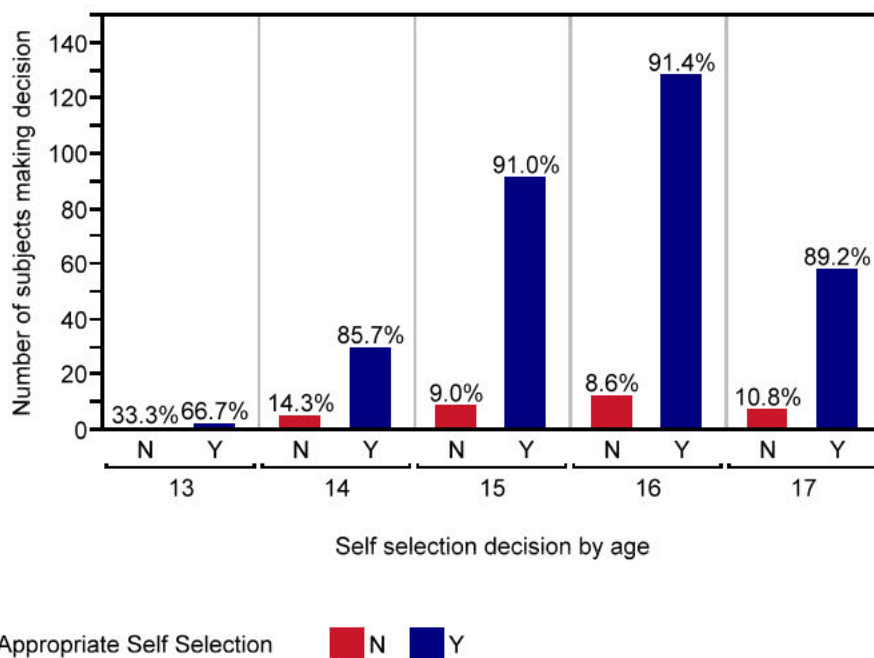


Table 16. Proportion of enrolled population that appropriately self-selected, by age

	11-13*	14*	15	16	17	Total
Number of Subjects	3	35	100	140	65	343
Appropriate Self-Selection	2 (66.7%)	30 (85.7%)	91 (91.0%)	128 (91.4%)	58 (89.2%)	309 (90.1%)
Lower 95% Confidence Bound for Proportion						86.4%

*For the pooled 11-14 year-old age group (38 subjects), the proportion with appropriate self-selection was 84.2% (32 subjects).

Additional analyses performed by the applicant include self-selection by investigational site and by prior history of EC use. Given that the UCSF site account for more than 90% of enrollment, I do not believe any analysis based on investigation sites is either necessary or meaningful. Self-selection decision stratified by prior history of EC use is summarized below in Table 17.

Table 17. Proportion of enrolled population that appropriately self-selected, for naive (first-time) users of EC, by age at screening

	11-13*	14*	15	16	17	Total
Number of Subjects	3	31	68	84	22	208
Appropriate Self-Selection	2 (66.7%)	27 (87.1%)	60 (88.2%)	73 (86.9%)	17 (77.3%)	179 (86.1%)
Lower 95% Confidence Bound for Proportion						80.6%

Medical officer comment:

With the exception of the very small group of 13-year-olds, all other age groups demonstrated acceptable level of appropriate self-selection decisions. Because the number of 11 to 13-year-olds enrolled was extremely small (n=3), it would be prudent to exercise caution in interpreting the results obtained for this age group in isolation.

Among the 343 enrolled subjects, 34 were said to have selected incorrectly to use Plan B One-Step. Among the 15 to 17-year-olds, approximately 10% did not make appropriate self-selection decision. The proportion of 14-year-olds not choosing correctly was 14.3%, although the size of this group was only about half of the 17-year-old group and much smaller than the 16-year-old group. The proportion in the 11-13-year-old group not making correct the correct self-selection decision was higher (33.3%) likely because of the very small sample size.

In their analysis, the applicant pooled the two youngest age groups and reported the overall appropriate self-selection by 11 to 14-year-olds, given the small sample sizes of these two groups. Among the 38 adolescents (three 13-year-olds and 35 14-year-olds), 32 (84.2%) made appropriate self-selection decisions.

To assess the importance of inappropriate self-selection, the reasons for inappropriate self-selection and the consequences of inappropriate self-selection must be considered. That said, the final study report does not present a comprehensive analysis of the reasons underlying these decisions. Additional insight into the adolescents' decision-making can be gained by evaluating the verbatim responses provided by these 34 adolescents to the question "Why did you come to the clinic today to get EC?" Among the potential responses (listed in Table 15), those corresponding to four categories indicate "inappropriate self-selection," based on the protocol-defined algorithm, which in turn is derived from directions of use and warning statements taken from Plan B One-Step's product label. Responses indicating inappropriate self-selection decision, despite having read the label, include those that indicate the subject 1) may be pregnant, 2) would like to use EC to prevent sexually-transmitted diseases, 3) would like to use EC for unprotected intercourse which occurred more than 72 hours prior to enrollment, and 4) would use EC as routine birth control. The responses given by these 34 subjects are presented below in Table 18.

Figure 6. Reasons for inappropriate self-selection, based on the applicant's analysis

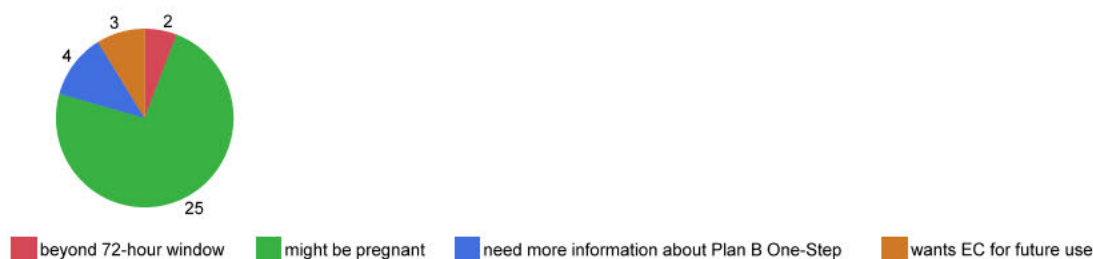


Table 18. Responses indicating inappropriate self-selection decisions

Subjects	Age	Reasons for wanting EC	Want to use EC	Pregnancy test	Stated they are pregnant?	Reasons for inappropriate self-selection
10025	14	condom mishap; might be pregnant	yes	no	no	might be pregnant
10028	14	condom mishap; might be pregnant	yes	no	no	might be pregnant
10034	17	condom mishap; might be pregnant	yes	no	yes	might be pregnant
10054	15	condom mishap;	yes	yes (+)	no	might be pregnant
10073	15	do not want to be pregnant	yes	no	yes	might be pregnant
10075	15	condom mishap	yes	no	yes	might be pregnant
10078	14	might be pregnant	yes	no	no	might be pregnant
10091	14	might be pregnant	no	no	no	might be pregnant
10096	17	unprotected sex; might be pregnant	yes	no	yes	might be pregnant
10098	17	might be pregnant	yes	no	yes	might be pregnant
10099	17	want birth control and to talk to provider	no	no	no	need more information about Plan B One-Step
10100	16	condom mishap; want to talk to provider	no	yes (-)	no	need more information about Plan B One-Step
10111	15	might be pregnant; want to talk to provider	no	no	no	need more information about Plan B One-Step
10112	15	want birth control to talk to provider	no	no	no	need more information about Plan B One-Step
10119	15	unprotected sex	yes	no	yes	might be pregnant
10137	16	unprotected sex	yes	no	yes	might be pregnant
10140	16	unprotected sex	yes	no	yes	might be pregnant
10145	16	unprotected sex	yes	no	yes	might be pregnant
10156	16	might be pregnant	yes	no	no	might be pregnant
10308	17	missed pill; might be pregnant	yes	no	no	might be pregnant
10348	17	might be pregnant	yes	no	no	might be pregnant
10351	17	unprotected sex 4 days ago	yes	no	no	beyond 72-hour window
10377	15	might be pregnant	yes	no	no	might be pregnant
10411	15	might be pregnant	yes	no	no	might be pregnant
10413	16	want to use EC for future use	yes	no	no	wants EC for future use
10521	13	unprotected sex 116 hours ago	yes	no	no	beyond 72-hour window
10530	16	might be pregnant	yes	no	yes	might be pregnant
10540	16	might be pregnant	yes	no	yes	might be pregnant
10564	14	might be pregnant	yes	no	no	might be pregnant
20003	16	want EC for future use	no	no	no	wants EC for future use
20006	16	want EC for future use	yes	yes (+) then (-)	yes	wants EC for future use
20014	16	unprotected sex; might be pregnant	yes	yes (+)	yes	might be pregnant
40004	16	might be pregnant	yes	no	yes	might be pregnant
40006	15	might be pregnant	yes	yes (-)	yes	might be pregnant

Medical officer comment:

As demonstrated by the subjects' responses to questionnaire on enrollment, the predominant reason for requesting EC (given by 25 of the 34 adolescents) was that they "might be pregnant." On further examination, however, many gave such a response despite the absence of concrete evidence (missed period and/or a positive pregnancy test). Among these 25 adolescents who had requested EC because they "might be pregnant," 12 stated later in the questionnaire that they were not pregnant, even though they had not done a pregnancy test. Another eight adolescents checked "yes" to the question "Are you pregnant?" despite not having done pregnancy tests or having had negative pregnancy tests. Only two adolescents (subjects 10054 and 20014) actually had had a positive pregnancy test when they expressed their desire for using EC. It is unclear whether the inconsistencies in the responses of these 25 adolescents indicate an incomplete understanding of the purpose of EC. It is likely that these adolescents considered themselves as "might be pregnant" simply from the acts of unprotected sex which prompted the clinic visit. Regardless of the reason for such inconsistent answers, what is clear is their understanding that their behavior had directly put them "at risk" for being pregnant. It is also clear that, had these twenty adolescents obtained and taken Plan B One-Step, the clinical consequences would have been minor. Two scenarios exist: if they are not already pregnant, taking EC could prevent them from becoming pregnant; if they are already pregnant, taking EC is not hazardous to their ongoing pregnancies.

Four subjects (10099, 10100, 10111, and 10112) stated that they would still like to talk to a provider even though they wanted to purchase Plan B One-Step. Other than expressing the desire for additional information about Plan B One-Step, the verbatim responses from these four subjects indicated that they were appropriate candidates for using the product. Also, the responses did not indicate that they had not understood the product label or would use the product incorrectly. Of note, these subjects were only given the outer carton and Drug Facts label to peruse before indicating their decision; it is likely that additional information they desired may be obtained from reading the package insert. In fact, these subjects made a correct decision; an OTC consumer has the freedom to decide to use, not to use, or to seek additional information. It would not be wrong to take any of these actions.

Two subjects (10351 and 10521) deemed to have made inappropriate self-selection decisions indicated that the acts of unprotected intercourse occurred beyond the 72-hour window. Subject 10351, a 17-year-old, had unprotected sex four days prior to enrollment; subject 10521, a 14-year-old, had unprotected sex almost five days prior to enrollment (116 hours). Although this use is outside of the approved therapeutic window, Plan B One-Step may be efficacious up to 120 hours after unprotected intercourse (see discussion under 5.3.2.5 Analysis of Secondary Endpoint). Therefore, these two subjects may still have derived benefit from using Plan B One-Step. With easier access to EC, it is conceivable that these adolescents would have used EC earlier than they did.

Three additional subjects (10413, 20003, and 20006) indicated that they wished to obtain Plan B One-Step for future rather than current use. These adolescents actually have the foresight in recognizing that, should they be in need of EC in the future due to unprotected or inadequately

protected intercourse, having the product already in their possession decreases the chance of delay in using the product. In fact, allowing these three adolescents to obtain EC for future use would be no different from what already takes in clinical practice. Prescribing EC in advance is commonly done by healthcare providers so that women have EC on hand when they need it. While Dr. Galson was concerned that EC should not substitute for routine contraceptive methods, I do not expect adolescents to resort to using EC as routine contraception because of potential undesired side effects such as irregular bleeding, prohibitive cost, and single-pill package configuration necessitating multiple visits to the pharmacy. The reader is referred to subsequent discussion regarding the data on repeat use of EC in Table 26 under section 5.3.2.5 Analysis of Secondary Endpoint.

Having considered the verbatim responses given by these 34 subjects, it appears that, according to the protocol-defined criteria, only seven subjects had self-selected to take Plan B One-Step inappropriately. These subjects and their reasons are presented in Table 19 below.

Table 19. Subjects who made inappropriately self-selection decisions per study protocol

Subject	Age	Reason for inappropriate self-selection
10054	15	+ pregnancy test
20014	16	+ pregnancy test
10351	17	Unprotected sex > 72 hours from enrollment
10521	13	Unprotected sex > 72 hours from enrollment
10413	16	Wants EC for future use
20003	16	Wants EC for future use
20006	16	Wants EC for future use

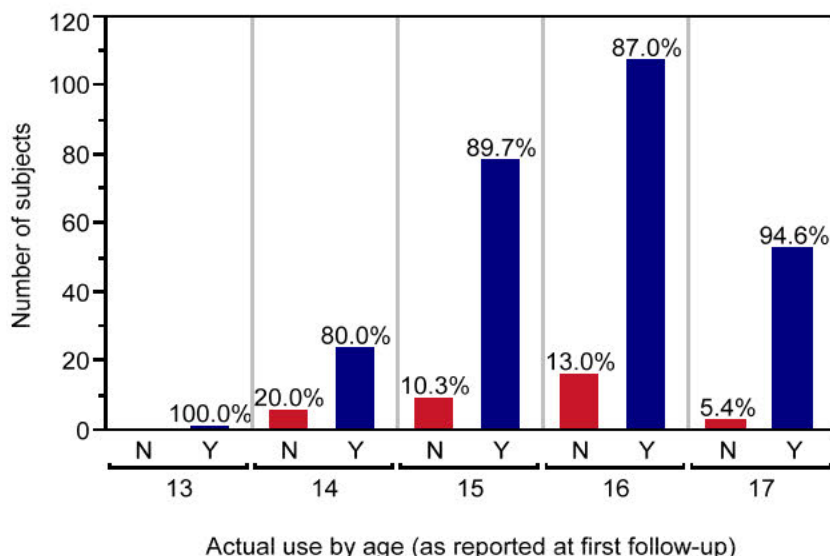
The first co-primary endpoint as calculated by the applicant, which is the proportion of subjects who correctly self-select to take the study product, should thus be adjusted. The proportion of subjects who selected inappropriately was 7/343, or 2.0%. Also, the proportion of subjects who appropriately self-selected should be 336/343, or 98.0% [95% confidence interval (96% - 99%)]. Therefore, per the protocol, this study has satisfactorily demonstrated that adolescents can indeed make appropriate decisions about whether to use Plan B One-Step.

Having said that, in the opinion of this reviewer, the only subjects who truly made inappropriate self-selection decisions are the first two subjects listed in Table 19 (#10054 and #20014) who had had positive pregnancy tests. Thus, this co-primary endpoint should be further adjusted. The proportion of subjects who selected inappropriately should be calculated as 2/343, or fewer than 1%. Correspondingly, the proportion of subjects who appropriately self-selected would be 341/343, or more than 99%.

Actual use

Of the 309 subjects who made appropriate decisions to use Plan B One-Step, 307 chose to take it and were dispensed the product. Of these, 305 subjects completed the first follow-up contact; among these 305 whose information was collected at the first follow-up contact, 297 subjects reported at their week-one follow-up contact, that they indeed had taken Plan B One-Step. The applicant's summary of the pattern of use by age demonstrated by these subjects is presented in Figure 7 and Table 20 below.

Figure 7. Actual use by age (Primary objective #2): of 297 treated subjects



Correctly used product? ■ N ■ Y

Table 20. Proportion of treated population demonstrating correct product use within 72 hours after intercourse, by age

	11-13*	14*	15	16	17	Total
Number of Subjects	1	30	87	123	56	297
Product Use Within 72 Hours	1 (100.0%)	24 (80.0%)	78 (89.7%)	107 (87.0%)	53 (94.6%)	263 (88.6%)
	Lower 95% Confidence Bound for Proportion					84.4%

*For the pooled 11-14 year-old age group (31 subjects), the proportion demonstrating correct product use was 80.6% (25 subjects).

The overall proportion of subjects who correctly took Plan B One-Step (within 72 hours following unprotected intercourse) was 88.6% (263 out of 297 subjects); the lower bound of 95%

confidence interval for this proportion was 84.4%. The proportions for individual age group ranged from 80.0% for 14-year-olds to 94.6% for 17-year-olds. Again, combining the two youngest age groups resulted in 31 subjects (one 13-year-old and 30 14-year-olds). The proportion demonstrating correct product use was 80.6% (25 out of 31).

With respect to prior experience with EC, the proportion of naïve EC users demonstrating correct use within 72 hours after intercourse is shown in Table 21 below. The overall proportion demonstrating correct use was 89.4% (ranging from 81.5% in 14-year-olds to 100% in 13- and 17-year-olds). For the pooled 11 to 14-year-old age group (28 subjects), the proportion demonstrating correct product use was 82.1% (23 subjects).

Table 21. Proportion of treated population demonstrating correct product use for naïve users of EC by age at screening

	11-13*	14*	15	16	17	Total
Number of Subjects	1	27	58	68	16	170
Product Use Within 72 Hours	1 (100.0%)	22 (81.5%)	53 (91.4%)	60 (88.2%)	16 (100.0%)	152 (89.4%)
	Lower 95% Confidence Bound for Proportion					83.8%

*For the pooled 11-14 year-old age group (28 subjects), the proportion demonstrating correct product use was 82.1% (23 subjects).

Medical officer comment:

Across the different age groups and overall, these data indicate that EC-naïve subjects did as well as EC-experienced subjects in being able to correctly use the study product. Therefore, these data can be taken to confirm that there is no learning curve associated with EC use. Indeed, to my knowledge, the Agency has not previously required that an OTC switch decision be contingent upon consumer data demonstrating appropriate usage of a single, fixed-dose, solid oral tablet.

Of the 307 subjects who had made appropriate self-selection decisions and were dispensed the study product, 10 subjects returned to the first follow-up reporting not having taken Plan B One-Step. Reasons for why they had not taken Plan B One-Step were unclear, but these subjects were excluded from the usage analysis by the applicant. Consequently, 297 subjects who actually took Plan B One-Step constitute the analysis cohort for actual use assessment. Of these 297 subjects who took Plan B One-Step, 34 subjects were coded by the applicant as having incorrectly used the product. They either took Plan B One-Step beyond the label-recommended 72-hour window, or they failed to follow-up within 10 days from the time they received the study product. The reasons for these subjects to be coded as having misused the product are presented in Table 22 below. In addition, this summary includes any adverse events reported by these 34 subjects.

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 Christina Chang, M.D., M.P.H.
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 Plan B One-Step (Levonorgestrel 1.5 mg)

Table 22. Subjects whose responses indicate incorrect product use

Subjects	Age	Used drug within 72 hours (elapsed time)		First follow-up within 10 days (elapsed days)		Adverse Events
		Yes	No	Yes	No	
10022	16		91 hours	3 days		
10032	17			8 days		metrorrhagia
10037	16				13 days	
10039	14			6 days		
10040	17		85.3 hours	4 days		
10059	15			3 days		
10074	15		74.5 hours	3 days		
10092	15	46 hours			12 days	
10125	15	20.5 hours			14 days	
10126	16		88.5 hours	4 days		
10131	14	40 hours			15 days	
10132	15				19 days	
10134	15		105 hours	7 days		
10148	16		93 hours		12 days	
10151	16	69 hours			14 days	
10153	16		74.5 hours	5 days		
10311	15		89.5 hours	6 days		metrorrhagia; vomiting; flu; took acetaminophen
10335	17		86 hours	3 days		
10336	16		93 hours	3 days		
10356	16		73 hours	3 days		
10366	14		75 hours	2 days		
10374	15		76 hours	3 days		
10379	15		118 hours	4 days		
10393	14	22 hours			12 days	
10409	16	43 hours			18 days	
10506	16		92 hours	2 days		
10517	16	28 hours			15 days	
10538	14		73.5 hours	8 days		
10553	16				12 days	
10562	16	68 hours			14 days	
20009	14	19 hours			12 days	
30001	16	17 hours			15 days	
30003	16	13.5 hours			19 days	
50001	16			9 days		

Medical officer comment:

The 10-day follow-up time frame is an arbitrary, protocol-defined criterion that highlights a dilemma for an actual use study. While the objective of an actual use study is to mimic the OTC, unsupervised setting as much as possible, data gathering would not be possible without a follow-up contact where information regarding product use is obtained from the subjects. In this case, such information includes the date/time when Plan B One-Step had been taken and any side effects the subject may have experienced. This follow-up contact serves no purpose other than to maximize data gathering for the study. In reality, such follow-up is clinically unnecessary unless the subjects have questions or experience adverse events for which the label recommends follow-up. As shown in Table 22 above, the study product is well tolerated; only two subjects reported adverse events, which consisted of irregular bleeding. In addition to metrorrhagia, subject #10311 also had flu-like symptoms which are most likely unrelated to the study drug.

Viewed in this light, subjects who were deemed per protocol to have misused the product only because of late follow-up in this study did not truly misuse the product. Therefore, those who took study product within 72 hours of unprotected sex but missed the 10-day mark for first follow-up may still be considered to have used the product correctly. That is, subjects 10092, 10125, 10131, 10151, 10393, 10409, 10517, 10562, 20009, 30001, 30003 (all highlighted in blue in Table 22) should be counted as having used the product correctly. Consequently, the overall proportion of subjects who correctly used the product should be 274/297, or 92.3% [95% confidence interval (88.6% - 95.0%)]. The amended correct use analysis based on age groups is shown below in Table 23. Again, this study has satisfactorily demonstrated that the enrolled adolescents can correctly use Plan B One-Step without provider counseling.

Table 23. Proportion of treated population demonstrating correct product use within 72 hours after intercourse, by age, adjusted

	11-13	14	15	16	17	Total
Number of subjects	1	30	87	123	56	297
Product use within 72 hours	1 (100%)	27 (90.0%)	80 (91.2%)	113 (91.9%)	53 (94.6%)	274 (92.3%)

In addition, this medical officer also conducted a sensitivity analysis using the intent-to-treat cohort (i.e., 307 subjects who were dispensed Plan B One-Step) by imputing the worst-case scenario. Note that 305 subjects completed the first follow-up contact, and 297 subjects reported having taken Plan B One-Step at this follow-up. If we assume that all eight subjects who reported not having taken Plan B One-Step at their one-week follow-up and the two subjects who were lost to follow-up would have taken the product incorrectly, then the proportion of treated population demonstrating correct product use within 72 hours would be 274/307, or 89.3%, which would still be acceptable. That said, it is important to note that the applicant did not collect information on the reasons why the eight subjects chose not to take the product once they were discharged from the study site. Without knowing the precise reasons for them not taking Plan B One-Step, results from such imputation may be difficult to interpret.

In response to Dr. Galson's criticism of the original Plan B consumer data (in that fewer than 5% of subjects in the Plan B actual use study were adolescents younger than 16 years of age), comparison can be made between these results and what was observed in the Plan B database. In study #9727, the actual use study conducted to support OTC switch of Plan B (sNDA 21-045, submitted April 16, 2003), the proportion of subjects who took the first dose of Plan B within 72 hours of unprotected intercourse was 92.4%. Concerns regarding cross-study comparisons notwithstanding, results from DR-LEV-302 thus compare favorably with those from the actual use study conducted to support OTC marketing of Plan B. The observation that adult and adolescent subjects used EC comparably well argues compellingly for removing age restriction at the point of purchase.

Finally, two of the ten subjects who had not taken study drug by the first follow-up reported having taken Plan B One-Step at the second follow-up contact (4 weeks after enrollment). These two subjects (subject #s 10136 and 10563) were coded as having used the product incorrectly because they did not take study product per protocol (within the 72 hours of unprotected intercourse which qualified the subjects for study enrollment). However, the study did not appear to query whether they had another episode of unprotected sex and used Plan B One-Step appropriately for that episode.

5.3.2.5 Analysis of Secondary Endpoint

A secondary analysis was conducted to assess the proportion of subjects taking Plan B One-Step within 120 hours of unprotected intercourse. As with product use information collected for the primary endpoint, this information was also based on subject reports at the week-one follow-up contact. The approved labeling recommends that Plan B One-Step should be "taken as soon as possible within 72 hours of unprotected intercourse." Nevertheless, single-dose, 1.5 mg levonorgestrel taken within 120 hours of unprotected intercourse was shown to also be effective to prevent unintended pregnancy (albeit less so than if given within 72 hours).³⁰ This regimen has also been accepted by many reproductive health professionals.^{31, 32} When the usage pattern is assessed by the 120 hour time frame, a slightly greater proportion of the treated population reported product use which still confer some efficacy benefit. Based on information collected at the first follow-up contact, 90.2% of the 297 treated subjects had taken Plan B One-Step within 120 hours following unprotected intercourse. Compared to the primary endpoint (using 72 hours from unprotected intercourse as a cut-off), 88.6% had taken Plan B One-Step. The proportion of subjects having taken study product within 120 hours by age, based on reports at the first follow-up contact, is shown in Figure 8 and Table 24 below. The applicant also notes that if the two youngest age groups (31 subjects aged 11 to 14 years) are pooled for this analysis, the proportion reporting product use within 120 hours of unprotected intercourse was 87.1%.

Figure 8. Proportion by age of treated population reporting product use within 120 hours after intercourse (of 297 treated subjects)

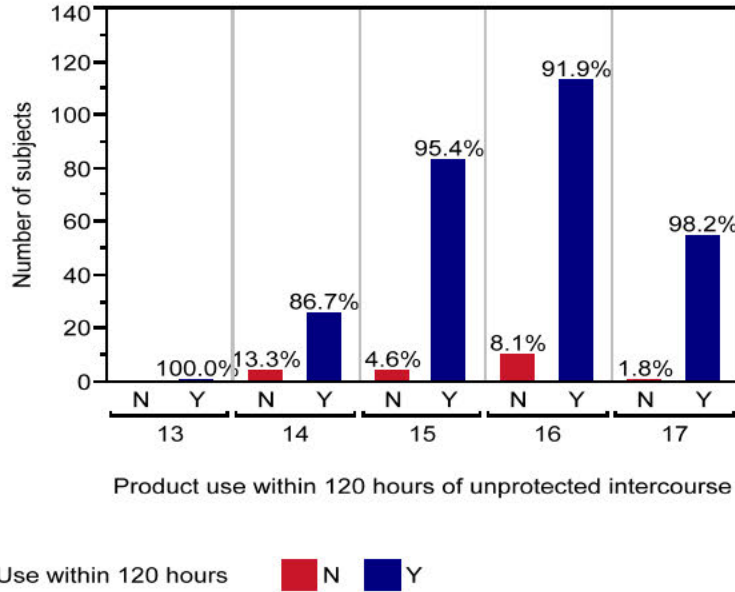


Table 24. Proportion of treated population reporting product use within 120 hours after intercourse, by age at screening

	11-13*	14*	15	16	17	Total
Number of Subjects	1	30	87	123	56	297
Product Use Within 120 Hours	1 (100.0%)	26 (86.7%)	83 (95.4%)	113 (91.9%)	55 (98.2%)	278 (93.6%)
	Lower 95% Confidence Bound for Proportion					90.2%

*For the pooled 11-14 year-old age group (31 subjects), the proportion demonstrating product use was 87.1% (31 subjects).

For EC-naïve users, the proportion of treated population taking Plan B One-Step within 120 hours of intercourse improves further. As shown in Table 25 below.

Table 25. Proportion of treated population reporting product use within 120 hours after intercourse for naive users of EC, by age at screening

	11-13*	14*	15	16	17	Total
Number of Subjects	1	27	58	68	16	170
Correct Product Use Within 120 Hours	1 (100.0%)	24 (88.9%)	56 (96.6%)	63 (92.6%)	16 (100.0%)	160 (94.1%)
Lower 95% Confidence Bound for Proportion						89.4%

*For the pooled 11-14 year-old age group (28 subjects), the proportion demonstrating product use was 89.3% (25 subjects).

Medical officer comment:

It should be noted that, despite Agency advice to pre-specify target thresholds for primary endpoints in DR-LEV-302, the applicant did not present a statistical plan that included stated thresholds. Nevertheless, analysis of product use at both 72 hours and 120 hours following unprotected intercourse indicates that older teens (15 to 17-year-olds) consistently demonstrate excellent ability to take EC within the therapeutic window, with appropriate product usage found in greater than 85% of subjects.

Difficulty enrolling younger adolescents and the resultant small number of 13-year-olds make meaningful interpretation of their data not feasible. The applicant thus appropriately pooled the younger adolescents (11 to 14-year-olds) for further analysis. Based on the applicant's analysis, the 72 hours and 120 hours time point respectively, Plan B One-Step was taken by 80.6% and 87.1% of these subjects. However, the satisfactory results seen in the adjusted analysis for the primary endpoint (product use within 72 hours of unprotected intercourse, Table 23) render this unadjusted secondary analysis relatively unnecessary and uninformative.

Another secondary objective was an evaluation of the incidence of repeat use of any EC during the 8-week follow-up period. The extent of repeat use in the Treated Population is shown in Table 26 below.

Table 26. Repeat use of EC in the Treated Population, by age (in years) at screening

Number of repeat uses	11 – 13 (N = 2)	14 (N = 30)	15 (N = 91)	16 (N = 127)	17 (N = 57)	Total (N = 307, % of N)
0	2	26	72	104	47	251 (81.8%)
1	0	1	12	19	6	38 (12.4%)
2	0	3	6	3	4	16 (5.2%)
3	0	0	1	1	0	2 (0.7%)

As shown in Table 26, the majority of subjects (251, 81.8% of 307) did not repeat EC use during DR-LEV-302. Among those dispensed Plan B One-Step, 56 subjects (18.2% of 307 subjects in the Treated Population) reported any additional EC use. A total of 38 subjects (12.4% of 307 in the Treated Population) reported using EC once after receiving Plan B One-Step, while 16 (5.2%

of 307) and 2 (0.7% of 307) reported using EC twice and three times during the study, respectively.

Medical officer comment:

For the three oldest age groups – 15-, 16-, and 17-year-olds – the results of the study indicate that repetitive EC use would be uncommon. This trend is not as clear-cut in 14-year-olds, probably due to their smaller group size. Nevertheless, it is reassuring that the number of subjects using three additional treatments of EC is very small for all age groups studied (from 0 to 1.1%) over the eight-week duration. Although the study duration is not long, considering the likely consequence of irregular bleeding associated with repetitive, intermittent progestin use and the prohibitive cost of EC (each course is more expensive than a monthly package of generic oral contraceptives), I would not expect to see long-term substitution of EC for routine oral contraceptives.

6 Review of Efficacy

The effectiveness of Plan B One-Step as emergency contraception has been already established for women of all reproductive ages. For additional details on efficacy for Plan B One-Step, the reader is referred to the clinical review by Dr. Daniel Davis for NDA 21-998, dated November 22, 2006.

7 Review of Safety

Safety Summary

Used as an emergency contraception, levonorgestrel has a wide margin of safety as demonstrated by the substantial postmarketing profile since the 1999 Rx approval. The totality of safety assessment for Plan B One-Step in this review is based on the following sources:

- Safety information included in DR-LEV-302
- Postmarketing safety data from Teva, from commercial launch of Plan B One-Step on July 10, 2009 to November 30, 2010
- Information from FDA's Adverse Events Reporting System (AERS) for Plan B, Plan B One-Step, and other levonorgestrel EC products from July 10, 2009 to September 30, 2010
- Information from the World Health Organization's (WHO) International Drug Monitoring Program for levonorgestrel EC products from July 10, 2009 to February 15, 2011

The safety findings from DR-LEV-302 are consistent with known profile of levonorgestrel. There were no unexpected serious adverse events and the results of DR-LEV-302 are sufficient to demonstrate that adolescents can appropriately and safely use Plan B One-Step. Analyses

performed on Teva's safety data as well as AERS and WHO revealed no unlabeled safety signals.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study DR-LEV-302 was a single-dose, multi-center, non-comparative, actual use study.

7.1.2 Categorization of Adverse Events

Adverse events were coded using MedDRA System Organ Class and Preferred Terms. A comparison between the coded terms and the verbatim reports from subjects was made; this medical officer finds the coding designations by the investigators appropriate.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling of data is not applicable since DR-LEV-302 is the only clinical study submitted in this application.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The principal deficiency cited by Dr. Galson for the actual use study conducted to support Plan B OTC marketing (NDA 21-045) was the small number of adolescents enrolled in the study. Specifically, only 29 adolescents aged 16 years and under were assessed. Of these 29, 20 subjects were 16-year-olds, and there were no data pertaining to adolescents younger than 13-years of age.

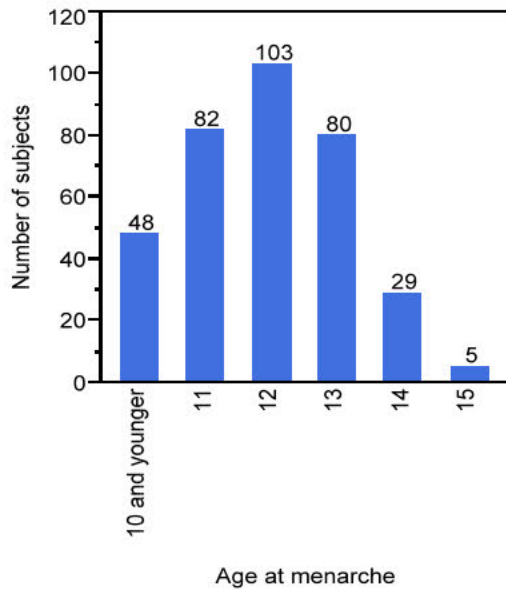
As requested by the Agency after input from Dr. Galson, DR-LEV-302 had protocol-defined minimum enrollment quota for each age group of 14 through 17 years of age; 25 subjects were to be enrolled in each age group.²⁰ Enrollment in DR-LEV-302 for each of these age groups more than satisfied these pre-specified quotas. The 14-year-old group consisted of 35 enrolled subjects, followed by 100 enrolled 15-year-olds, 140 enrolled 16-year-olds, and 65 enrolled 17-year-olds. Of note, DR-LEV-302 study protocol was amended to terminate enrollment of 17-year-olds, following the July, 2009 approval of OTC status for Plan B One-Step for consumers 17-years and older.³³ Thus, DR-Lev-302 included 278 adolescents aged 16 and younger, and nearly half of them (138, 49.6%) were younger than age 16.

Despite expanding study enrollment to five geographically diverse sites, only three subjects aged 13 years were enrolled in DR-LEV-302 over a two-year study period. Unable to enroll any subject under 13 years of age, the applicant sought to have the enrollment quota for this age group (25 subjects aged 11 to 13 years, inclusive) lifted. In 2010, rationales were presented by the applicant to support removing the quota for the youngest age group. These rationales are based on available data demonstrating the infrequency of these young adolescents seeking contraceptive health counseling. They included:

- The average American female does not reach menarche until age 12.³⁴ Premenarchal girls are not at risk for pregnancy and therefore have no reason to use Plan B One-Step.
- The vast majorities of females 11 to 14 years old are not sexually active and therefore are not at risk for pregnancy and have no reason to use Plan B One-Step.³⁵⁻³⁸
- The pregnancy rate in females 11 to 14 years old is low.³⁹
- Even in settings where there is pharmacy access to Plan B for people of all ages, the proportion of all Plan B One-Step consumers who are young teens is minimal.
- The likelihood of females 11 to 13 years old presenting to one of the actual use study sites across the country requesting emergency contraception within 72 hours after unprotected intercourse is expected to approach zero.
- It is not appropriate or consistent with the nature or design of this actual use trial to advertise for subjects. Enrollment is therefore dependent on the number of teenagers who spontaneously present to the investigative sites requesting emergency contraception for use in the subsequent three days. The infrequency of this occurrence does not support a minimum enrollment requirement for teens 13 years old and younger.

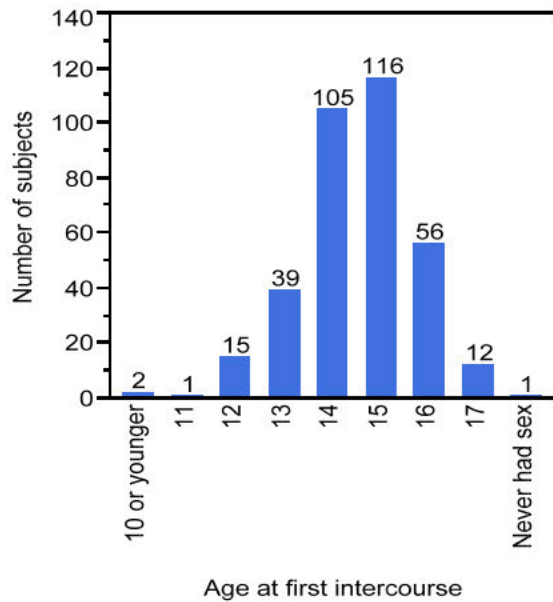
FDA accepted the applicant's rationales justifying the removal of protocol defined enrollment quota for the 11- to 13-year-old group.²⁸ Subsequently, the DR-LEV-302 study protocol was amended to remove this enrollment quota.⁴⁰ Findings from DR-LEV-302 now appear to validate these rationales. Based on the analysis datasets provided in this application, distribution of the subjects' age at menarche is shown in Figure 9, while the distribution of the age at first sexual intercourse is shown in Figure 10. The reported age at menarche is consistent with the average age at menarche based on data from the latest available National Health and Nutrition Examination Survey (NHANES, 2002) conducted by the Center for Disease Control and Prevention (CDC).³⁴

Figure 9. Age at menarche, DR-LEV-302 population



Compared to results obtained by other surveys (such as the Youth Risk Behavior Surveillance conducted by the CDC)³⁵⁻³⁸, the reported age at first sexual intercourse is also comparable. According to results of Youth Risk Behavioral Surveillance System's 2005 and 2007 surveys^{37, 38}, 3.7% and 4% of teens surveyed reported having first sexual activity before age 13 years, respectively. Meanwhile, the National Survey of Family Growth³⁶ indicated that 4.5% of teens surveyed reported having first sexual activity before age 13. In contrast, 5.2% of the subjects in DR-LEV-302 reported first sexual intercourse before age 13. Therefore, based on the age at menarche and age at first sexual activity, it would be reasonable to assume that the population enrolled in DR-LEV-302 reflects the adolescent population in general. The findings from DR-LEV-302 should thus be generalizable.

Figure 10. Age at first intercourse, DR-LEV-302 population



7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in DR-LEV-302.

7.3.2 Nonfatal Serious Adverse Events

One serious adverse event was reported in this study. Subject #01-0502 reported a miscarriage following the use of Plan B One-Step. Her case narrative is summarized below under section 7.6 Additional Safety Evaluations.

7.3.3 Dropouts and/or Discontinuations

This is a single-dose study.

Since only two subjects were lost to follow-up, the completion rate for DR-LEV-302 (99%) was excellent. Of the 307 subjects who were dispensed the study product, all but these two subjects completed the first follow-up contact. At the first follow-up, 297 subjects reported having taken Plan B One-Step; the study did not collect information on why the other eight subjects chose not to take the study product.

7.3.4 Significant Adverse Events

Pregnancies were confirmed in seven subjects who took Plan B One-Step. All seven subjects used Plan B One-Step correctly, i.e., they took Plan B One-Step within 72 hours of unprotected sexual intercourse. The seven pregnancies were listed in Table 27 below, and more details for each pregnancy are provided following my comment below. It was not surprising that all seven pregnancies were reported from the UCSF site, given that it enrolled more than 90% of the subjects.

Table 27. Pregnancies reported in DR-LEV-302

Site-Subject	Age (years)	Used Plan B One-Step within 72 hours of unprotected intercourse	Elapsed time from unprotected sex to product intake	Pregnancy status	Pregnancy dating	Possible conception dates based on ultrasound findings
10107	16	Yes	25.5 hours	Termination	By 8-week/3-day ultrasound	Up to one week after the index episode of unprotected sex
10131	14	Yes	40.0 hours	Termination	By 13-week/1-day ultrasound	Possibly already one-week pregnant when she took Plan B One-Step (too early for self-detection or positive pregnancy test)
10302	17	Yes	40.0 hours	Termination	By 7-week ultrasound	Up to two weeks after the index episode of unprotected sex
10362	16	Yes	45.0 hours	Termination	By 7-week ultrasound	Up to 4 days after the index episode of unprotected sex
10384	16	Yes	27.0 hours	Live birth at 36+ wks	By 26-week ultrasound	Up to one month after the index episode of unprotected sex
10405	16	Yes	35.0 hours	Ongoing pregnancy	By 7-week ultrasound	Up to 9 days after the index episode of unprotected sex
10502	16	Yes	33.5 hours	Miscarriage	Negative pregnancy test 2 weeks after taking Plan B One-Step but positive 3 weeks after taking Plan B One-Step	Unsure; her last menstrual period was not provided and the ultrasound findings did not specify an estimated gestational age (likely did not show a viable embryo)

*index episode of unprotected sex: the episode of unprotected sex that prompted the clinic visit to seek EC

Medical officer comment:

Table 27 was compiled by this medical officer by including information from Table 30 of the final study report and the case narratives in the case report form (CFR). A discrepancy between data presented by the applicant's summary and the CRF for subject 01-0131 was noted by this medical officer. The CRF indicated that she had taken the study product, although Table 30 of the study report indicated that she had not.

Of the 297 subjects who actually used the study product, seven pregnancies were documented. It should be noted that all seven subjects who became pregnant during the study demonstrated appropriate product use, taking Plan B One-Step within 48 hours of unprotected intercourse. The data do not support any relationship between correctly taking EC and age, or between pregnancy incidence and age.

Whether these pregnancies occurred as a result of lack of efficacy is unclear. The applicant did not explore whether these pregnancies were conceived as a result of the acts of unprotected sex that prompted the clinical visits to request EC. Such analysis may have been possible if the study had collected data to allow for a more accurate assessment of conception dates with respect to the timing of Plan B One-Step administration for these pregnancies. Specifically, this study did not collect information on whether these subjects had any acts of unprotected sex subsequent to the index episode for which they requested EC. Also, detailed menstrual history (e.g., length of cycles, regularity of the cycles, etc.) from these subjects was not included in the CRFs provided. These limitations preclude a more precise determination of gestational age for these pregnancies. Consequently, this medical officer relied on estimated gestational age provided by ultrasound findings for each subject to derive a range of possible dates of conception for each pregnancy. It should be noted that with advancing gestational age, the reliability of ultrasound dating decreases. While first trimester ultrasound findings are generally quite reliable (within \pm one week of true gestational age), estimation of gestational age by a 26-week ultrasound (i.e., for subject 10384) is much less so (greater variability, with a range of \pm 2-3 weeks). Therefore, without a more detailed coital history, determination of gestational age for each pregnancy is imprecise.

Based on the estimates of gestational age, it would be difficult to establish that these pregnancies occurred as a result of lack of efficacy for Plan B One-Step for the index episodes of unprotected sex. In fact, given the range of possible conception dates derived from ultrasound findings, it is quite likely that four of these pregnancies were conceived after the index episodes of unprotected sex (subjects 10107, 10132, 10384, and 10405). Thus, I would not attribute these pregnancies to lack of efficacy for Plan B One-Step. For subject 10362, since the conception date suggested by ultrasound-estimated gestational age lies within four days of the index episode of unprotected sex, her pregnancy may be considered treatment failure. As to subject 10131, who likely was one-week post-conception when she took Plan B One-Step, her pregnancy should not be considered a treatment failure. Her use of Plan B One-Step should not be deemed inappropriate, however, since the pregnancy was too early to have caused any symptoms, such as nausea or a missed period. With regard to subject 10502, there is insufficient information available to judge whether her pregnancy was a result of treatment failure since gestational age could not be determined.

These data provide further support for the efficacy of Plan B One-Step; out of 297 subjects who took Plan B One-Step, only one pregnancy (subject 10362) resulted from possible treatment failure. Furthermore, I find the observation that four pregnancies were likely conceived subsequent to the index episodes of unprotected sex underscores the need for easier access to

EC. Had these subjects had EC on hand, these pregnancies (which subsequently resulted in two abortions and two teen births) may have been prevented.

Subject 10107 (pregnancy, terminated)

This is a nulligravid 16-year-old Latina female. She too reported having used oral contraceptives, condoms, and EC in the past. She had unprotected sex on September 10, 2009 and took Plan B One-Step on September 11, 2009. At follow-up #3 (conducted on November 2, 2009), she stated that a pregnancy test she performed on October 14, 2009 had been positive. On November 2, 2009, a transvaginal ultrasound revealed an intrauterine pregnancy measuring 8 weeks and 3 days. She underwent an uncomplicated surgical procedure for pregnancy termination on

(b) (6)

Subject 10131 (pregnancy terminated)

This is a nulligravid 14-year-old African-American female. She had never used hormonal contraceptives or condoms previously but reported having used EC in the past. She had unprotected sex on March 7, 2010, and took Plan B One-Step on March 8, 2010. She reported no health issues at the first follow-up contact (conducted on March 23, 2010); she also reported not having done any pregnancy tests at this contact. At follow-up #2 (conducted on April 9, 2010, she stated that a pregnancy test she performed on March 31, 2010 had been positive. On May 17, 2010, a transvaginal ultrasound revealed an intrauterine pregnancy at 13 weeks and 1 day. She underwent an uncomplicated surgical abortion performed

(b) (6)

Subject 10302 (pregnancy terminated)

This is a nulligravid 17-year-old Latina female. She also reported having used several contraceptive methods (pills, patch, condoms, and withdrawal) and EC in the past. She had unprotected sex on March 22, 2009 and took Plan B One-Step on March 24, 2009. At the third follow-up contact (conducted on May 19, 2009), she reported having had a positive pregnancy test, which she performed on May 1, 2009. On May 7, 2009 a transvaginal ultrasound revealed an intrauterine pregnancy at 7 weeks. She underwent an uncomplicated surgical abortion on

(b) (6)

Subject 10362 (pregnancy terminated)

This is a nulligravid 16-year-old Latina female. She had never used any hormonal contraceptives but had experience using EC in the past. She had unprotected sex (condom broke) on July 4, 2009, and took Plan B One-Step on July 6, 2009. At the third follow-up (conducted on August 31, 2009), she stated that a pregnancy test she performed on August 4, 2009 had been positive. A transvaginal ultrasound done on August 13, 2009 revealed an intrauterine pregnancy at 7 weeks. She underwent an uncomplicated pregnancy termination on

(b) (6)

Subject 10384 (live birth)

This is a G₁P₀₀₁₀ 16-year-old Latina female with an obstetrical history significant for one previous pregnancy termination. She had never used any hormonal contraceptives or condoms prior to enrollment, but reported that she had used EC in the past. She had unprotected sex on October 8, 2009, and took Plan B One-Step on October 9, 2009. At follow-up #3 (conducted on

December 3, 2009, she stated that a pregnancy test done on November 25, 2009, had been positive. Per the CRF, she had an ultrasound on April 20, 2010, showing the estimated gestational age to be 26 weeks. The subject delivered on [REDACTED] (b) (6) at approximately 36.5 weeks gestation without complication. Per the last follow-up contact (conducted on December 10, 2010), the infant (almost [REDACTED] (b) (6) months old) was reported to be in good condition.

Subject 10405 (live birth)

This is a G₁P₀₀₁₀ 16-year-old Caucasian female with an obstetrical history significant for one previous pregnancy termination. She reported having used oral contraceptive pills and condoms prior to enrollment, but she had never used EC in the past. She had unprotected intercourse (condom broke) on August 17, 2010, and took Plan B One-Step on August 18, 2010. At follow-up contact #3 (conducted on October 13, 2010), the subject stated that a pregnancy test performed on September 22, 2010 had been positive. On September 30, 2010, a transvaginal ultrasound revealed a 7-week gestation, giving her an expected delivery date of May 20, 2011. The subject delivered on [REDACTED] (b) (6) without complication.

Subject 10502 (miscarriage)

This is a nulligravid 16-year-old Latina female. She reported having used oral contraceptives and EC in the past. She had unprotected sex on September 20, 2009, and took Plan B One-Step on September 21, 2009. At the second follow-up contact (conducted on October 15, 2009), she stated that a pregnancy test performed on October 13, 2009 had been negative. At the third follow-up contact (conducted on November 13, 2009), she reported a positive pregnancy test which had been performed on October 27, 2009. On [REDACTED] (b) (6), she presented to the emergency room with bleeding and lower abdominal pain. A diagnosis of spontaneous abortion was made; she was discharged with instructions to follow-up at Planned Parenthood.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The original study report indicated that, of the 297 subjects who used study drug, 43 subjects reported a total of 67 adverse events (AEs). No subjects reported more than three AEs. Following internal audit of the source data, the applicant updated the safety information on July 25, 2011, to include two additional subjects who took the study drug (the safety population), and to add three non-serious adverse events. Thus, the 45 subjects in this study reported a total of 70 AEs.

An updated summary of the AEs reported by $\geq 1\%$ of subjects in the safety cohort is displayed in Table 28 below.

Table 28. Commonly reported adverse events by the safety population

Adverse event (preferred term)	N (%)
Headache	8 (2.7)
Nausea	8 (2.7)
Menstrual irregular	6 (2.0)
Vaginal bleeding	4 (1.3)
Pelvic pain	4 (1.3)
Influenza	3 (1.0)
Vulvovaginal mycotic infection	3 (1.0)
Spotting vaginal	3 (1.0)
Dizziness	3 (1.0)
Abdominal pain upper	3 (1.0)
Fatigue	3 (1.0)
Vomiting	3 (1.0)
Nasopharyngitis	2 (0.7)
Dysuria	2 (0.7)
Concussion	1 (0.3)
Gastroenteritis viral	1 (0.3)
Abdominal distention	1 (0.3)
Rash	1 (0.3)
Hot flush	1 (0.3)
Vaginitis bacterial	1 (0.3)
Back pain	1 (0.3)
Urinary tract infection	1 (0.3)
Decreased appetite	1 (0.3)
Vaginal discharge	1 (0.3)
Vomiting in pregnancy	1 (0.3)
Abortion spontaneous	1 (0.3)
Anxiety	1 (0.3)
Breast tenderness	1 (0.3)
Infectious mononucleosis	1 (0.3)

The most frequently reported AEs were headache, nausea, and menstrual irregularity. Of the 70 total AEs, 18 appear to bear no relation to the study drug (e.g., concussion, influenza, nasopharyngitis, vaginitis, etc.). Only one AE was of a serious nature (miscarriage); see discussion under section 7.3.2. The relationship of this AE to Plan B One-Step could not be definitely established. The reader is referred to the discussion under section 7.3.4 for additional details of this case. As to remaining 52 AEs, their nature and frequency appear to be consistent with the known side effect profile of the drug. Therefore, the safety findings reported here do not present any new issues and further support the favorable safety profile of levonorgestrel EC.

7.5 Other Safety Explorations

No other safety explorations are performed.

7.6 Additional Safety Evaluations

None.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In response to the Agency's request, Teva submitted via a NDA amendment on April 6, 2011, an assessment on the abuse potential of Plan B One-Step.

The applicant queried the Drug Abuse Warning Network (DAWN) database. A search on data available for 2004 to 2009, this query yielded no reports for "contraceptives" in this time frame. When searched under the category of "progestins," the applicant identified a rate of 0.1 cases per 100,000 persons for the year 2008. No cases were reported for 2004 to 2007 or 2009. It should be noted that the category of progestins includes different progestins used predominantly for different indications (i.e., hormone replacement therapy in peri- or postmenopausal women and combination oral contraceptives for women of reproductive age). Thus, the proportion of DAWN reports associated with levonorgestrel EC alone was likely vanishingly small.

The applicant also performed a query from National Poison Data System (NPDS), which is maintained by the American Association of Poison Control Centers (AAPCC). It appears that the applicant's analysis was limited to reports received by NPDS during 2008 to 2009. Analysis of reports received in 2009 focused on substances categorized as "hormones and hormone antagonists." This category of hormones and antagonists includes androgens, corticosteroids, estrogens, insulin, selective estrogen receptor modulators, thyroid preparations, as well as oral contraceptives and progestins. Based on the total number of substances reported in all exposures, this substance category ranked #16 (receiving 2.08% of reports) among the top 25 substance categories most frequently involved in human exposure, behind categories such as "vitamins" (#13, 2.54%), "bites and envenomations" (#14, 2.46%), "antimicrobials" (#15, 2.46%). Importantly, the hormone/antagonist substance category ranked substantially below "analgesics" (#1, receiving 11.75% of all reports in NPDS) and "cosmetics/personal care products" (#2, 7.75%). Data from the year 2008 pertaining to the hormone/antagonist category resulted in similar ranking. Considering that the entire hormone/antagonist category consists of numerous drug products, drawing any conclusions on specific risks incurred by single ingredient levonorgestrel products proves difficult. Based on this NPDS information, one can reasonably conclude that Plan B One-Step is not associated with risks associated with overdosing. Although it is unclear why data from only 2008 and 2009 were selected for the applicant's analysis, inclusion of NPDS data from additional reporting years would likely not have changed this assessment.

Based on their assessment of the DAWN and AAPCC data, the applicant concluded that Plan B One-Step is unlikely to be associated with abuse potential or overdosing. This medical officer agrees with the applicant's conclusion that Plan B One-Step is unlikely to be a candidate for drug abuse or misuse based on these analyses. I also agree with the applicant that additional detailed analysis will not yield any meaningful information and thus would not be warranted.

8 Postmarket Experience

In a joint safety review finalized on June 27, 2011, the Agency summarized the postmarketing experience for Plan B One-Step from commercial product launch in 2009 to January 31, 2011.⁴¹ The review identified no safety concerns that required further assessment.

In addition, the applicant provided postmarketing experience for Plan B One-Step based on analyses of three separate pharmacovigilance databases. The original NDA submission included only Teva's postmarketing safety data. Consistent with our practice for reviewing all Rx-to-OTC switches, the Agency requested safety information be provided based on analyses of the FDA's Adverse Events Reporting System (AERS) and the World Health Organization's (WHO) International Drug Monitoring Program (Vigibase). Teva's analyses on these two databases were submitted in an amendment to this supplemental application on April 6, 2011. These are discussed separately below. It should be noted that postmarketing reports are limited by their spontaneous and voluntary nature and that establishing causal relationship to drug exposure often proves difficult. That said, the extent of the postmarketing safety information summarized in sections below supports the known excellent safety profile of levonorgestrel EC.

8.1 Teva's Postmarketing Experience

The applicant provided an analysis of their postmarketing safety database for Plan B One-Step. The time interval examined began with the time of approval on July 10, 2009 through November 30, 2010. Since the safety of Plan B One-Step in adults and 17-year-old adolescents is not in question, the analysis was restricted to reports for patients aged 9 to 16 years of age. Although the age of 9 years was selected as a reasonable lower age bound for the search based on the age of menarche in the United States, the youngest reporter was 13 years of age.

A total of 332 events were reported by 186 individual young women regarding Plan B One-Step. This represents 2.4% of all events reported for the time period in question (13,881 events). However, to put the number of reports in better perspective, it is helpful to refer to the distribution information provided by the applicant (see Table 3). From commercial launch of Plan B One-Step on July 10, 2009 to November 10, 2010, a total of (b) (4) doses of Plan B One-Step were distributed by prescription to adolescents aged 16 and younger (note that distribution to clinics such as Planned Parenthood is not accounted for in this calculation). In order to harmonize the reporting period being assessed (for both AE reporting and sales information), only two-thirds of the Rx distribution in the month ending December 10, 2010

should be included in the total adolescent distribution above (since analysis of the safety data was limited to November 30, 2010 rather than December 10, 2010). Therefore, total adolescent distribution during the time period concordant with collection of the safety data is estimated to be (b) (4) unit doses. While the extent of repeat-dosing in the real-world is unknown, we can estimate that 186 cases were reported to the pharmacovigilance database out of (b) (4) unit doses used by adolescents (a reporting rate of 0.13%), if we make the assumption that no adolescents used more than one dose of Plan B One-Step. Factoring in the potentially sizable distribution to adolescents who obtain the product through clinics (clinic distribution for the same period was (b) (4) unit doses, calculated from (b) (4) unit doses + two thirds of (b) (4) unit doses), the AE reporting ratio in adolescents aged 16 and younger could be almost negligible. Table 29 below presents the frequency of events by System Organ Class (SOC) by age group.

Table 29. Summary of AEs by age, by SOC, July 10, 2009 to November 30, 2010

AE by SOC	11-13 years old	14 years old	15 years old	16 years old	Total (all ages)
Reproductive system and breast disorders	1	14	54	111	180
Gastrointestinal disorders	1	9	28	47	85
Nervous system disorders	1	3	11	19	34
General disorders and administrative site conditions	0	1	3	9	13
Musculoskeletal and connective tissue disorders	0	0	3	4	7
Renal and urinary disorders	0	0	0	4	4
Pregnancy, puerperium and perinatal conditions	0	1	1	1	3
Respiratory, thoracic and mediastinal disorders	0	0	0	2	2
Injury, poisoning and procedural complications	0	0	0	2	2
Psychiatric disorders	0	0	0	1	1
Skin and subcutaneous tissue disorders	0	0	0	1	1
Total	3	28	100	201	332

*listed in descending order based on total number in SOC

The two SOC's associated with the most number of AEs (reproductive system and breast disorders and gastrointestinal disorders) are further summarized by MedDRA preferred terms (PT), by age, as shown below in Table 30.

Table 30. Summary of adverse events by age, by preferred terms, July 10, 2009 to November 30, 2010

AE by PT	11-13 years old	14 years old	15 years old	16 years old	Total (all ages)
Reproductive system and breast disorders	1	14	54	111	180
Breast pain	0	0	0	2	2
Breast tenderness	0	1	1	5	7
Menorrhagia	0	0	2	1	3
Menstruation delayed	0	1	9	9	19
Menstruation irregular	1	7	31	67	106
Pelvic pain	0	2	5	18	25

Vaginal discharge	0	2	6	8	16
Vulvovaginal discomfort	0	0	0	1	1
Vulvovaginal pain	0	1	0	0	1
Gastrointestinal disorders	1	9	28	47	85
Abdominal discomfort	0	2	1	0	3
Abdominal distention	0	0	0	5	5
Abdominal pain	1	2	6	9	18
Abdominal pain lower	0	0	3	1	4
Abdominal pain upper	0	0	2	5	7
Diarrhoea	0	0	1	0	1
Haematemesis	0	0	0	1	1
Nausea	0	3	9	10	22
Vomiting	0	2	6	16	24

Three of the events were categorized by the applicant to be “serious and unlabeled,” – vomiting blood (haematemesis), positive home pregnancy test (drug ineffective, pregnancy after post-coital contraception). All three events were reported by a single individual, a 16-year-old.

Medical officer comment:

Although the applicant did not provide distribution information further stratified by age group, it appears that the number of AEs increase with increasing age. This is expected if use of Plan B One-Step increases with increasing age, which is a reasonable assumption.

The adverse events reported to the applicant do not raise any new or significant safety concerns. Of note, the event “hematemesis” has been reported for both Plan B and Plan B One-Step products. The reader is referred to FDA’s postmarketing safety review for Plan B One-Step for detailed assessment on 18 consumer reports of hematemesis (from July 2007 to December 2010).⁴¹ It is important to note that these cases reporting hematemesis were poorly documented (i.e., no quantification of the amount of blood in the emesis) and lacked medical confirmation (all were consumer reports, without verification of any resultant hospitalization or transfusion). FDA did not view these cases as a significant signal. Furthermore, FDA did not detect an age-related clustering in these cases.

8.2 AERS Data

The applicant queried AERS for information relating to Plan B, Plan B One-Step, and other levonorgestrel-containing EC products. The covered time frame for this query was from July 10, 2009 to September 30, 2010.

In AERS, there were a total of 71 cases among women of all ages reporting 303 adverse events for Plan B and Plan B One-Step, and an additional 28 cases reporting 66 adverse events for other levonorgestrel ECs. Of the total 369 AEs reported, 134 (36%) correspond to events listed in the Warnings and Precautions or Adverse Events sections of the current U.S. product labeling. Additionally, 69 reported AEs (19%) were directly related to lack of efficacy of the drug (e.g., “pregnancy after post coital contraception,” or “drug ineffective”). Of the remaining 166 AEs,

eight were reported at a rate of greater than 1% of total AEs reported (N = 4 or more). They are listed in Table 31 below. The relationship of any of these AEs to levonorgestrel, if any, is unclear and would be difficult to ascertain given the limitations of postmarketing reports.

Table 31. Unlabeled Adverse events reported to AERS (rate of ≥ 1%)

Adverse events	Number of reports
Spontaneous abortion	22
Back pain	6
Premature baby	5
Congenital anomaly	4
Crying	4
Haematemesis	4
Haemorrhage	4
Suicidal ideation	4 (one initial and three follow-up reports of the same case)

The applicant identified no additional issues following the exploration of drug-drug interaction and drug-disease interaction. Therefore, analysis of AERS postmarketing data does not raise any new safety issues.

In response to FDA’s information request, the applicant also queried AERS for MedWatch reports relating to adolescents aged 16 years and younger who have used levonorgestrel EC. This search identified four cases among 71 cases reported by women of all ages. All four adolescent cases were from 15- and 16-year-olds. Three of them took either Plan B or Plan B One-Step, while one took the generic product, Next Choice. These cases are summarized below in Table 32 below.

Table 32. AERS reports for levonorgestrel EC in adolescents aged 16 years and younger

ISR #	Age	Product	AEs	Serious outcome (reason)?	Medically confirmed?	Comment
6330193	16	Plan B	Hematemesis, nausea, vomiting, menstruation irregular	Yes (“other”)	No	Reported being seen in the emergency room and resolution of hematemesis
6408593	16	Plan B One-Step	Hematemesis	Yes (“other”)	No	Positive pregnancy test 2 weeks after taking EC
6583665	15	Next Choice	Hypersensitivity reactions	No	No	Reported being treated by doctor
7002342	15	Did not take any EC	Emotional distress	No	No	Report described distress stemming from difficulty in obtaining EC

Of interest to this supplemental application is the last case, ISR # 7002342, reported on September 16, 2010, by a 15-year-old who needed EC after an episode of unprotected sex. This adolescent described the difficulty in accessing EC because of her age. She was erroneously

advised by the pharmacist that Plan B was only available OTC to women 18 and older (more than one year after the labeling change allowing OTC sale to 17-year-olds). After obtaining a prescription for Plan B from her doctor, she returned to the same pharmacy and was informed that they were out of stock. She asked a friend's mother to drive her to another pharmacy, only to be told that Plan B was no longer available. It appears that neither pharmacy contacted her doctor to inquire about dispensing the generic equivalent of Plan B or Plan B One-Step, since she described herself as having "no options." Expanding the OTC target population to all females of reproductive age as the applicant is proposing can eliminate some of the barriers experienced by this adolescent. The earlier she could obtain EC, the greater the efficacy for preventing pregnancy. The reader is also referred to additional discussion on the implication of EC's short therapeutic window in my rationales for recommending approval for this supplemental application (rationale #2 under Section 1.2 Risk Benefit Assessment).

These safety data should be considered in the context of distribution data provided by the applicant. The distribution data specified in Table 3 of this review indicate that (b) (4) treatments (both Plan B and Plan B One-Step) were prescribed during approximately the same time period (July 9, 2009 to September 10, 2010) to adolescents aged 16 years and younger (these products were available OTC to those 17 years and over starting July 9, 2009). It is also likely for the true overall exposure to levonorgestrel EC to be even higher since the applicant's distribution data did not account for the sales of generic products. Given that ISR case #7002342 never took EC, only three adolescent cases reporting adverse events are identified in AERS. Viewed in this light, three cases out of at least (b) (4) treatments yield a reporting rate of 0.0017% for Plan B and Plan B One-Step in adolescents aged 16 years and younger. Furthermore, none of the reported adverse events appeared to be unique to the adolescent population. Assessment of hematemeses (the reason for case #6330193 and #6408593 to be deemed of having "serious outcome") is already discussed in section 8.1 above.

Based on these data, review of AERS database does not support any new or serious safety issues for levonorgestrel EC products.

8.3 WHO Data

Teva presented an assessment of Vigibase data pertaining to levonorgestrel 1.5 mg for EC reported during the time from July 10, 2009 to February 15, 2011. The search yielded a total of 969 reports.

A total of 369 cases reported 969 AEs. Of these 969 events, 265 (27%) are already listed in the Warnings and Precautions or Adverse Events sections of the U.S. product labeling. An additional 252 AEs (26%) are directly related to lack of efficacy (pregnancy). Among the remaining 452 AEs, those reported at a rate of greater than 1% of total AEs (N = 10 or more) were: spontaneous abortion (42), uterine haemorrhage (16), and hemorrhage (16). Again, these were directly related to pregnancy. The remaining 378 events all occurred at a rate of less than 1%.

A total of five cases were identified to be adolescents aged 16 and under. Since Vigibase also include AERS reports, two of the five adolescents were already assessed under the AERS section. The remaining three adolescents reported breast disorder, ectopic pregnancy, and fetal abnormality (not otherwise specified), none of which are age-specific adverse events. As with the AERS data, no specific inferences can be made after assessing drug-drug interaction and drug-disease interaction.

9 Appendices

9.1 Literature Review

The applicant references 23 publications in support of this supplemental application. Those deemed not directly pertinent to this supplement are excluded by this reviewer from further discussion. They include:

- Three of these publications describe efficacy data submitted to support the original NDA approvals for Plan B and Plan B One-Step;^{7, 30, 42}
- Three references pertain to validated instruments used to assess health literacy in adults and adolescents as well as adolescent decision-making;⁴³⁻⁴⁵
- A Federal Register notice permitting certain combined oral contraceptives to be used as postcoital emergency contraception.⁴⁶
- One reference was a review of epidemiologic data to support the safety of combination oral contraceptives.⁴⁷
- One publication was a Letter to the Editor detailing a case report of a 26-year-old female who presented with retinal vein thrombosis, which was thought to be associated with her intake of emergency contraception.⁴⁸ The EC product implicated in this case, however, is a combination product containing 500 µg norgestrel and 50 µg ethinyl estradiol. It is well-recognized that venous thromboembolic events are associated with the estrogen component in hormonal contraceptives. The amount of ethinyl estradiol in this preparation is higher than that present in most oral contraceptive products currently prescribed. Also, the progestin involved here is not identical to levonorgestrel. It is unlikely that this case would be pertinent to the safety profile of levonorgestrel-only EC products. Importantly, postmarketing data pertaining to Plan B or Plan B One-Step have not signaled an increase in venous thromboembolic events.

A total of 14 citations remain and are considered pertinent to the subject of this application. This medical officer has also identified 17 additional publications pertaining to levonorgestrel EC use and adolescents. These 31 references fall into several categories and are discussed further below.

Surveys-type studies

Six reports involve surveys conducted to assess adolescents' attitudes and understanding of EC use.^{29, 49-53} Some of these studies used the Plan B (rather than Plan B One-Step) label. However,

these studies are included in this review because the Plan B and Plan B One-Step labels are virtually identical with exception of dosing directions.

Raymond et al. 2002 interviewed 663 women, among whom 76 were aged 12 to 16, to assess comprehension of the prototype OTC Plan B label.⁵³ As the key label comprehension study used to support the OTC switch proposal for Plan B, the study's design and questionnaire received the Agency's input, and findings from this study have already been reviewed by the Agency as part of the Plan B OTC switch program. Eleven communication objectives relevant to safe and effective use of Plan B were assessed. Nine communication objectives were understood by greater than 80% of the subject (five were understood by > 90% of the subjects). Two other communication objectives ("Plan B should not be used for regular contraception" and "Plan B should not be used by women with unexplained vaginal bleeding") were understood by 67% and 75% of the subjects, respectively. The results indicate that by reading the prototype label, women could understand key information conveyed in the label and were found by the Agency to lend support for the eventual Plan B switch in 2006. However, the adolescent population was not separately analyzed in this study.

Raymond et al. 2009 summarized the data from a second label comprehension study presented to the Agency in support of this supplemental application.²⁹ Results were discussed in section 5.3.1 DR-LEV-301 (Label Comprehension Study). Refer also to the DNCE social scientist's review. It should be noted that, comparing data presented in DR-LEV-301 (Raymond 2009) with data presented in Raymond 2002 (discussed in the preceding paragraph), adolescent subjects enrolled in DR-LEV-301 demonstrated equally good (or better) understanding as adult subjects for key communication objectives in the label. Indeed, the least understood communication objective in the adult study ("Plan B should not be used for regular contraception", understood by 67% of subjects) was understood by 90% of 12- to 14-year-old subjects and by 94% of 15- to 17-year-old subjects in DR-LEV-301.

Cremer et al. 2009 conducted a label comprehension study via surveys in 1085 New York City adolescent females between ages 12 and 17 years to assess their comprehension of OTC Plan B label.⁵⁰ Of all subjects completing the study, 861 were 16 years of age or younger; however, a separate analysis of adolescents 12 to 16 years of age was not reported in the article. The communications objectives examined and the proportion of subjects demonstrating understanding were:

- Plan B is a method of preventing pregnancy (92%)
- Plan B has to be taken within the first 72 hours after unprotected intercourse (83%)
- If you are already pregnant, emergency contraception will not be effective (87%)
- Emergency contraception will not protect against HIV/AIDS (95%)
- Emergency contraception should not be used as a method of long-term birth control (85%)

The authors concluded that the adolescent subjects enrolled demonstrated understanding of key elements of the label to ensure safe and effective use. Results from this study are largely

consistent with findings of 2002 and 2009 publications by Raymond et al.^{29, 53} However, it should be noted that the conduct of this study differs from the two Raymond et al. studies. First, the participants were not screened for health literacy prior to their interview. Second, the interviews were not conducted in private; the investigators observed that some teens might have been less likely to take time to answer the questions carefully. Some participants were also allowed to compare answers with peers. Although the size of this study is large, all these factors can limit the validity of the study results.

Mollen et al. 2008 published results of a survey based on interviews of healthy, urban-dwelling 15-to 19-year-old African American adolescents to assess their attitudes regarding EC use.⁵² The final sample included young women who reported sexual activity (N = 16) and those who did not (N = 14), as well as those who had been pregnant (N = 5) and those who had not (N = 25). Despite the recruitment effort (the authors screened close to 100 potential subjects), the final sample consisted of only 30 adolescents. Based on the verbatim answers given, the authors observed that these adolescents have limited baseline knowledge about EC. Specifically, although 94% (15 out of 16) of the sexually active participants had heard of EC, 40% of these subjects were unable to answer follow-up questions such as the timing for EC use. In addition, the adolescents' attitudes toward EC can be influenced by opinions of those to whom they are close, such as female friends, mothers, or sisters. Since the study did not provide the subjects any information (such as an approved Plan B label) prior to the interviews, the study did not evaluate whether providing EC labels to the subjects would have improved their knowledge or changed their attitudes about EC. The authors acknowledge that the study was too small to allow drawing meaningful conclusions or generalizing of the results.

Krishnamurti et al. 2008 reported findings from a survey study in adolescent females aged 13 to 19 years.⁵¹ Interviews and follow-up surveys were conducted to assess how Plan B availability would affect the adolescents' decision making in two-stages. Semi-structured interviews were first conducted in 30 subjects to assess their decision-making related to whether to engage in sex, to use condoms, or to use Plan B. Concluding that the complexity and variety of the adolescents' thinking made it difficult to aggregate the views expressed, the investigators undertook a larger, structured survey in 125 adolescent females aged 12 to 18 years. Importantly, citing the FDA's concerns laid out in the 2006 Rx/OTC dual approval action, the study stratified the subjects into two groups (< 16 years, N = 41 vs. ≥ 16 years, N = 84) for comparison. The authors observed largely comparable decision-making processes between the two groups, but noted the following statistically significant differences between younger and older adolescents: the younger adolescents were 1) less likely to know about Plan B, 2) less likely to cite pleasure as a reason to have sex, 3) more likely to cite physical discomfort as a reason to avoid sex, and 4) more likely to think that greater EC availability would increase unprotected sex in their peers although they would not expect themselves to engage in more unprotected sex. The investigators concluded that their data mitigate the concern that younger teens would not behave like older teens. They recommend that "whatever reasoning led FDA to approve OTC availability for older teens should apply to younger teens as well."

Ahern et al. 2010 reported findings of self-administered, anonymous surveys completed by 100 adolescent females aged 14 to 19 years to examine their knowledge and awareness of EC.⁴⁹ Subjects in this study attended a University Teen Clinic in Hawaii which serves a racially diverse, underserved, and disadvantaged population. The subjects either had experienced an unintended pregnancy or were at high risk for an unintended pregnancy. Specifically, the mean age at coitarche was 14.7 years; 95 (95%) of subjects were sexually active at the time of the study, among whom 65 (68.4% of 95) were currently pregnant or had been pregnant in the past. Data from the survey suggest that adolescents have lower rates of EC awareness compared to rates reported in adults. Results showed that 56 (56% of study sample) respondents were aware of EC, and 39 (69.6% of 56) could correctly identify an EC method. The authors appear to characterize EC as “America’s best kept secret” and fault the Agency’s previous action resulting in age restriction as a barrier to EC access for adolescents.

Clinical studies

There have been a number of clinical studies conducted to assess the impact of EC advance provision on sexual/contraceptive behaviors. Since this efficacy application concerns adolescents, this literature review will exclude studies that were conducted primarily in adult women outside the U.S.,⁵⁴⁻⁵⁷ or studies that used EC regimens containing ethinyl estradiol (which may have a sufficiently different side effect profile from levonorgestrel-only regimens to impact on use behavior).^{58, 59}

A total of 17 publications describe U.S. clinical studies which assessed levonorgestrel-only EC taken by adolescent subjects.^{9-11, 60-73} These are discussed individually in more detail below.

Raymond et al. 2003 reported the results of an actual use study which was conducted to support the original Plan B OTC switch application. The design of this study simulated the OTC setting and is similar to DR-LEV-302, which now provides pivotal support to this supplemental application. A total of 665 women were enrolled, of whom 5% (29) were 16 years and younger. The findings reported here have undergone exhaustive FDA review. It should be noted that results of DR-LEV-302 compare favorably with findings reported in this paper. For a more detailed comparison between these two studies, the reader is referred to the medical officer comment under section 5.3.2.4 Analysis of Primary Endpoints.

Data from randomized, controlled studies:

Gold et al. 2004 reported findings from the first randomized controlled trial enrolling adolescents and young women from a hospital-based adolescent clinic. This trial assessed whether advance provision of EC corresponded with an increase in risk-taking behavior among 301 sexually active females 15 to 20 years of age.⁹ Participants were randomized into either receiving EC (the study commenced using the Yuzpe regimen, and then switched to Plan B subsequently) at enrollment (N = 150) or receiving instruction on how to obtain EC (N = 151). Adolescents using long-acting contraceptives (such as intrauterine device, subdermal levonorgestrel implant (Norplant), or depot medroxyprogesterone injections (Depo-Provera) at the time of enrollment were excluded. However, oral contraceptive pill users were eligible. Monthly telephone interviews were conducted for six months post-enrollment to collect data on

self-reported unprotected intercourse and condom use. Importantly, the interviewers were blinded to the participants' group assignment. The authors found no significant differences between groups in reported unprotected intercourse within the past month or at last intercourse. At the six-month follow-up, more adolescents in the advance provision group reported condom use in the past month compared to the control group (77% vs. 62%, $p = 0.02$). There were also no significant differences by group in hormonal contraception use reported in the past month or at last intercourse. The investigators conclude that providing advance EC promotes earlier use of EC without negatively impacting the ongoing use of condoms or hormonal contraception.

Belzer et al. 2005 conducted a randomized control trial to assess advance EC provision and contraceptive behavior in 160 adolescent mothers aged 13 to 20 years.⁷⁰ The subjects were recruited from the participants in case management services administered by the California Child Welfare Services in the City of Los Angeles. They were randomized into receiving a monthly supply of Plan B for this 12-month study ($N = 82$) or controls ($N = 78$). The control group received handouts on primary contraception methods as well as the proper use of EC and how to access EC after unprotected sex. Interviews were conducted with the subjects at the baseline, 6-month and 12-month time points. No significant differences were found between the groups with respect to condom use at either the 6-month or 12-month follow-up. However, the advance provision group was more likely to have used EC than the control group at both the 6-month (83% vs. 11%, $p = 0.0001$) and 12-month (64% vs. 17%, $p = 0.0028$) follow-up. The advance provision group also reported engaging in more unprotected sex at 12 months (69% vs. 45%, $p = 0.0439$), but had numerically fewer pregnancies (7 vs. 18, $p = 0.0681$). It should also be noted that this study did not control for differences in behavior at baseline (the control group reported more likely to be sexually active than the intervention group), which may have biased the findings. The authors recommended that youths receiving advance supply of emergency contraception also receive close medical follow-up to reinforce condom use and primary contraception.

Raine et al. 2005 conducted another randomized controlled trial and assessed advance EC provision on reproductive health outcomes (pregnancy and STI).¹⁰ This single-blinded study enrolled 2117 young women aged 15 to 24 years who were not desiring pregnancy nor using long-term hormonal contraception. Importantly, 483 subjects (25%) were 15-to 17-years old. Participants were randomly assigned to one of three groups: 1) pharmacy access to EC without the need to obtain a prescription from healthcare provider ($N = 814$), 2) advance provision of 3-packs of Plan B ($N = 826$), and 3) standard clinic access as control ($N = 310$). Shortly after commencing the study, enrollment into the control group was eliminated to avoid financially disadvantaging the participants (EC access through the two interventions was free of charge). The participants returned for follow-up visits (92% completion rate; equal proportion among groups); telephone interviews were conducted for those who did not return to the clinic (3.7% of subjects). The results showed that women in the advance provision group were more likely to use EC than controls (37.4% vs. 21.0%, $p < 0.001$) even though the reported frequency of unprotected intercourse was similar.

With respect to the primary outcomes, 8% of participants became pregnant and 12% acquired an STI. Compared with controls, women in the pharmacy access and advance provision groups did not experience a significant reduction in pregnancy rate (odds ratio for pharmacy access group 0.98, 95% CI 0.58-1.64; odds ratio for advance provision group 1.10, 95% CI 0.66-1.84). The authors noted that high EC use in the clinic access group may have contributed to the lack of difference in observed pregnancy rates. Also, relative to the controls, women in the two intervention groups also did not have increased STIs (odds ratio for pharmacy access group 1.08, 95% CI 0.71-1.63; odds ratio for advance provision group 0.94, 95% CI 0.62-1.44). There were also no differences in patterns of contraceptive or condom use or sexual behaviors by study group. The authors concluded that restricting EC access to clinics is unnecessary given the lack of clear evidence of increased risky behavior associated with pharmacy access to or advance provision of EC.

Harper et al. 2005 conducted a secondary analysis focusing on the adolescent population enrolled in the Raine et al. 2005 trial.⁶¹ Adolescents comprised 45.5% (N = 964) of the original trial cohort; for this analysis, the authors stratified the adolescents into three groups: young adolescents (< 16 years, N = 90), mid adolescent (16-17 years, N = 393), and late adolescents (18-19 years, N = 481) before making comparisons with adults (20-24 years, N = 1153). Completion rate for adolescents enrolled was 93% (893), not different from the overall adult cohort or among the three adolescent treatment groups. The pharmacy access arm had 372 adolescent subjects, advance provision arm had 372 adolescent participants, and the clinic access arm had 142 subjects. During the course of the study, 36% (320) of all adolescents used EC, with a significantly higher proportion reporting use in the advance provision group than in pharmacy access or clinic groups (44%, 30%, and 29%, respectively, $p \leq 0.001$). In general, EC use among the youngest adolescents (38%) was the same as the middle group (38%), and slightly higher than the older adolescent group (33%). In addition, 62% of adolescents who used EC reported using it once, similar to 65% in the adult population. Also, 93% of adolescents who took EC used it correctly (N = 295), including 95% in the advance provision group (N = 157). Among the youngest adolescents (< 16 years), 97% (N = 30) of those who used EC reported correct use. With respect to frequency of unprotected intercourse, condom use, STI acquisition or pregnancy, the authors did not observe differences in behavior by study arm. The authors conclude that younger adolescents with enhanced access to EC used the method more frequently when needed, but did not compromise their use of routine contraception nor increase their sexual risk behavior.

Walsh et al. 2006 also conducted a randomized, controlled trial to assess EC use.⁷³ Over 9000 women aged 15 to 45 years were randomized to receive either one packet of Plan B or an identical packet containing EC information only. Follow-up interviews were conducted six months later in a subset of 1130 women (of whom 53% received EC and 47% received information only) selected to optimize age and ethnicity distribution to collect information on EC use and attitudes toward EC. The investigators found that women given EC in advance were significantly more likely to have used EC (19%) since their study visit than women given information only (12%) ($p = 0.0009$). There were no statistically significant differences between the groups concerning the reasons given for taking EC, side effects, or pregnancy. The subjects generally exhibited positive attitudes toward using EC, with 93% indicating that having EC on-

hand was a good idea. The authors conclude the study demonstrated that access to EC encourages use but does not increase risk-taking behavior. However, the findings in this study should be considered with caution given the methodological flaws (fewer than 25% of randomized subjects were available for data collection subsequently). This study has been consistently excluded from many of the meta-analyses conducted due to design flaws.

Raymond et al. 2006 reported results of a randomized controlled trial conducted to assess two strategies of providing EC accesses to sexually active women aged 14 to 24 years.¹¹ A total of 1490 subjects were randomly assigned to receive increased access (two packages of Plan B at enrollment with unlimited resupply at no charge, N = 746) or standard access (as needed at usual charges, N = 744). Among the increased access group, 35 were 14- and 15-year-olds and 178 were 16- and 17-year-olds. Of the standard access group, 34 were 14- and 15-year-olds and 161 were 16- and 17-year-olds. Both groups of participants were instructed to take the pills as a single dose of 1.5 mg levonorgestrel (two tablets at once) as soon as possible after unprotected intercourse. Follow-up visits were conducted at 6 and 12 months after enrollment. In addition, at approximately 2, 4, 8, and 10 months after enrollment, the participants were contacted by mail or email to complete a short survey about contraception use in the two weeks prior. Results showed that attrition rate was low for both groups (5% of intervention group and 6% of control group), which differs from other trials investigating EC advance provision (which had loss of follow-up rates up to 40%). Among the subjects who used EC, those in the advance provision group used EC significantly sooner after sex (median time of EC intake from unprotected sex 12 hours vs. 36 hours in the control group, $p < 0.01$). The incidence of pregnancy was similar in the two groups (hazard ratio 0.95, 95% confidence interval 0.68 – 1.33). The combined outcome of sexually transmitted infections (STI, Chlamydia, Gonorrhea, and Trichomonas) was also similar, (hazard ratio 0.91, 90% CI 0.66 – 1.26). Although the data were not reported separately for adolescents, age was said to not be significantly related to sexually transmitted infection risk. Finally, the participants' self-reported coital activity and contraceptive use did not differ significantly by group at 5-7 and 12-14 months after enrollment. The authors conclude that enhanced access to EC substantially increased use of the method and had no adverse impact on the risk of sexually transmitted infections. However, the data failed to show a benefit in decreasing pregnancy rates. A likely hypothesis to explain the observed lack of benefit in reducing pregnancy rates in this study, according to the authors, is the underutilization of EC. More than one third of women in both treatment groups admitted to having had unprotected sex at least once without using EC afterward. Furthermore, the authors note that underestimation of this proportion is likely because of poor recall, denial, and the desire to please the researchers. They thus conclude that despite increased access, many risky coital acts remained “uncovered” by EC.

Rocca et al. 2007 examined attitudes and EC use patterns among 2117 women aged 15 to 24 years in a randomized trial evaluating three strategies of accessing EC.⁶⁴ The participants were randomly assigned to pharmacy access (i.e., no prescription was required), advance provision of three packs of Plan B, or standard clinic access as control. All three groups received EC free of charge; six months later, 1950 subjects completed a follow-up questionnaire (92% completion rate). Consistent with other trials evaluating advance provision, the investigators report that 571

(29%) subjects used EC during the study period. Those who received EC in advance were most likely to use it (37.4%) than women in the pharmacy (24.2%) or clinic (21.0%) arms ($p < 0.001$ for pair-wise comparisons). Women in the advance provision group were also more likely to take EC within 24 hours of the coital act than women in the clinic arm (odds ratio 2.43, 95% CI 1.24-4.80).

In addition, 14% of participants reported not using EC on at least one occasion when they thought it might be called for. The most common reason given was that getting EC was too much trouble or too inconvenient (23%). This response varied significantly among study arms, with 42%, 30%, and 11% giving this response in the clinic, pharmacy, and advance provision arms, respectively ($p < 0.001$). The authors support expanding EC access, since women can access it in the way that can optimize use.

Ekstrand et al. 2008 conducted a randomized controlled trial to evaluate an intervention involving advance provision of EC to 420 Swedish adolescents aged 15 to 19 years (intervention group $N = 214$, control group $N = 206$).⁷¹ While both groups received EC on request, the teens assigned to the advance provision group received one additional dose, condoms, and information leaflet about EC and condom use. Follow-up was done via telephone interviews at 3-month and 6-month post-enrollment. At both follow-up contacts, girls receiving EC in advance were almost twice likely as those in control group to have used EC. The investigators also found that adolescents who had been provided with EC in advance used it approximately 12 hours sooner after unprotected intercourse compared with controls. There were no significant differences found in the use of regular hormonal contraceptives or condoms at either follow-up.

Raymond et al. 2008 conducted a secondary analysis based on results of an earlier trial reported in Raymond et al. 2006.⁷² Noting more common EC use among women who had increased EC access in the menstrual cycles where the pregnancies occurred, the authors investigated the implications of free, advance EC provision on pregnancy risk behavior. Results from Raymond et al. 2006 showed that EC was used in 17 of the 74 menstrual cycles leading to pregnancy (23%) in the intervention group but in only two of the 74 pregnancy cycles (3%) in the standard access group ($p = 0.002$). This study was undertaken to more closely examine the timing of EC use, patterns of coitus, and use of other contraceptive methods during the cycles ending in pregnancy. The authors observed that in the advance provision group, 16 women had 17 pregnancies in menstrual cycles in which EC was used. Of these 17 pregnancies, 5 (29%) and 7 (41%) were considered probably and possibly to have resulted from EC failure, respectively. In the standard access control group, two pregnancies occurred in two women in cycles in which EC was used; only one pregnancy was judged possibly to have resulted from EC failure. The authors calculated that the proportion of cycles that were entirely unprotected and in which more than one coital act reportedly occurred was significantly higher in the intervention group than in the control group ($p = 0.017$). The authors conclude that results are consistent with the hypothesis that the intervention to increase women's access to EC was followed by an increase in unprotected or under-protected sex. That said, the authors urge caution in interpreting the findings given some caveats. First, some of the judgments on whether individual pregnancies occurred as a result of EC failure may be incorrect. Second, they stress that no increase in STIs

(arguably a more worrisome outcome per the authors) were observed. Third, the results apply to the specific intervention (advance EC provision free of charge) and should not be generalized to other interventions to increase EC access, since EC treatments are unlikely to be free of charge to most women. The authors also recommend that public health resources would likely be more productive in encouraging women to either begin to use or to improve their use of more efficacious routine contraceptive methods immediately after taking EC.

Sander et al. 2009 published their findings of another secondary analysis on the control group participants from the Raymond et al. 2006 trial described above.⁶⁵ Subjects in this study were restricted to the cohort of women randomized to the standard access group in Raymond et al. with any follow-up data (N = 718). Bivariable analysis showed no association between recent EC use and time to pregnancy (hazard ratio, HR, 0.85, 95% CI 0.48 – 1.52) or ever EC use and time to pregnancy (HR 0.85, 95% CI 0.53 – 1.37). Bivariable analysis also showed no association between recent EC use and time to STI diagnosis (HR, 1.09, 95% CI 0.60 – 1.99) or ever EC use and time to STI diagnosis (HR 0.91, 95% CI 0.54 – 1.60). Based on the findings, the authors suggest that EC is underutilized in this population, and that further efforts should be aimed at educating the young women about sufficient pregnancy/STI prevention activities.

Weaver et al. 2009 reported a third secondary analysis based on data from Raymond et al. 2006 trial to examine the effect of advance EC provision on contraceptive attitude and behavior.⁶⁹ Their analysis was based on interview data from 565 women in the advance provision group (of 723, 78%) and 573 women in the standard access group (of 717, 80%) from the cohort of 1490 women in the original study. The authors observed that women given EC in advance were significantly more likely to report that they had ever used EC because they did not want to use either condoms or another contraceptive method ($p < 0.001$). In addition, authors claimed their analysis showed that the effect of increased access to EC on pregnancy risk was inversely related to a woman's "aversion to pregnancy." For example, among women with an estimated "aversion to pregnancy" score at the 90th percentile (i.e., the most "averse" women), advance provision increased the risk of pregnancy relative to standard access (hazard ratio 1.73, 95% CI 1.01-2.98). However, the authors further state that among women with an estimated "aversion to pregnancy" score at the 10th percentile (i.e., the least "averse" women), advance EC provision decreased the risk of pregnancy relative to standard access (hazard ratio 0.64, 95% CI 0.39-1.04). It is unclear to this medical officer why this preceding statement was made in the publication, because the 95% CI, by including 1, showed no statistical significance. The authors interpret the findings as evidence that effect of unrestricted access may not be uniform across the study population. Nevertheless, results of this study should be interpreted with caution, given some of the limitations acknowledged by the authors. First, the endpoints were not pre-specified (unlike the original study, as reported in Raymond et al. 2006). The analysis here could have thus been influenced by knowledge of the primary study result, although the authors denied selective reporting of study results. In addition, as acknowledged by the authors, providing women with unlimited, free supplies of EC in advance of need is not how EC is accessed currently. Therefore, the same limitation identified in Raymond et al. 2008 (which also reported results from secondary analyses of the same data from Raymond et al. 2006) also applies here; results

reported in this study do not necessarily generalize to other types of increased access intervention.

Schreiber et al. 2010 conducted a randomized, controlled, feasibility study of 50 postpartum teens aged 14 to 19 years to assess whether postpartum advanced supply of EC helps to prevent repeat pregnancies of close proximity.⁶⁶ The scope of this study was small; its purpose was to explore the potential for conducting a larger, future randomized control trial in this population. The subjects were randomized into advance supply group (N = 23) and the routine care group (N = 27). At the routine postpartum visit, subjects in the advance supply group received one dose of Plan B One-Step in addition to a prescription for the primary contraceptive method of their choice; they were also told that they could receive unlimited supply of EC if requested. Follow-up interviews were conducted at 6 weeks, 3, 6, and 12 months post enrollment. Results showed that EC was used during the one-year study by 12 subjects in the intervention group and eight subjects in the control group. At the 12-month interview, there were three pregnancies (13%) in the intervention group and eight pregnancies (30%) in the control group. Although this difference in the number of pregnancies is not statistically significant, the authors concluded that the design and setting of this study sufficient to give consideration to conduct a randomized controlled trial that is adequately powered to examine efficacy of advance EC provision.

Data from observational studies:

Stewart et al. 2003 reported the results of a retrospective chart review to examine the impact of using EC on reproductive health outcomes.⁶⁸ The study involved 182 subjects aged 13 to 21 years attending an urban, hospital-based adolescent clinic; 92 had been prescribed EC at an identifying clinic visit, while 90 aged-matched controls (who had a clinic visit within 7 days of the EC subject's index visit) received routine gynecologic care. The investigators recorded pregnancies and STIs that were documented for the 12-month period prior to the identifying visit, and tracked the records of each subject's reproductive health care over the following 24 months. Baseline characteristics of the two groups were similar: surveys showed no significant difference between the groups for mean age at coitarche (mean age at first intercourse for the entire sample was 14.5 ± 1.7 years). There was also no difference between the EC and control groups with respect to the number of lifetime partners. No significant differences were found between EC and control subjects in the prevalence of STIs (Trichomonas, Gonorrhea, or Chlamydia), although more controls subjects were diagnosed with Chlamydia than EC subject ($p = 0.03$). EC subjects were no more likely to have a positive pregnancy test documented than control subjects ($p < 0.23$) during the 24 months after index visit. Noting the limitations of inherent study design, the authors conclude that EC use was not associated with poorer reproductive health outcomes (such as an increased incidence of pregnancy or STIs). The authors noted that no differences were found in the occurrence of pregnancy at any point in the study, which led them to conclude that EC use was neither more common among adolescents who experienced pregnancies and STIs, nor was its use associated with subsequent higher incidence of pregnancy. The authors offered two possible hypotheses to account for this less-than-expected EC usage in the treatment group. One explanation is that EC is often used only as a back-up method when another contraceptive method fails. The second explanation is that the majority of subjects used EC only one time, while using more reliable methods the rest of the time, which

would not significantly increase their odds of pregnancy. It should be noted however, that in prospective, randomized clinical trials assessing advance EC provision, a difference in EC usage is typically observed in the advance provision group.

Harper et al. 2004 conducted an open-label, observational study to assess the tolerability and usage of Plan B in 52 adolescents aged 13 to 16 years who attended family planning clinic.⁶² Participants were given the first dose of Plan B in the clinic, and were instructed to take the second dose in 12 hours. They were also asked to record the date/time of taking the second dose as well as bleeding or side effects in a diary until the follow-up visit three weeks after enrollment. The authors reported that 98% (51/52) of subjects took the second dose of Plan B as instructed, and that 94% (49/52) of subjects reported no problems in following directions. Nausea, fatigue, headache, and diarrhea were the most commonly reported side effects, but the reported side effects did not differ by age. There was also no difference in the mean reported duration of menses for the subjects before and after treatment. The authors conclude that adolescents were capable of following simple instructions for correct use of Plan B and experienced no serious adverse events or menstrual disturbances.

Sidebottom et al. 2008 examined the circumstances prompting adolescents to request EC at school-based clinics.⁶⁷ The claims database was queried for EC-related visits at five school clinics in a Midwestern urban area during the 2002-2003 school year; a chart review was conducted for all medical records identified to have had an EC request. The authors identified 113 instances in which a student requested EC and 109 cases in which Plan B was dispensed. These instances involved 91 students ranging from 14 to 20 years of age. There was only one 14-year-old; most students requesting EC were 15 to 17 years of age. The most frequently cited reasons for requests were using no protection (37.2%), condom mishap (27.4%), questionable protection from hormonal method (23.9%), and anxiety despite adequate protection (10.5%). There were 16 students who requested EC more than once during the study period; the authors characterized their reasons for request as more often reported contraceptive failure or improper use rather than by absolute lack of protection. Of the 75 instances in which either no protection or only a condom had been used, 51 (68.0%) were known to culminate in the subsequent initiation of a hormonal method. The authors conclude that EC appears to fill a critical need for some adolescents by providing crucial protection against pregnancy while sexually active adolescents were in the process of finding a contraceptive method compatible with their personal preference.

Hensley Alford et al. 2010 reported the results of a retrospective cohort study to evaluate differences in EC use between adolescents (11 to 17 years old) and young adult women (18 to 24 years old) in an insured, population-based cohort.⁶⁰ The investigators identified a cohort of 334 females 11 to 24 years of age who filled at least one Preven and/or Plan B prescription between 1997 and 2006; the study included 40 adolescents and 304 young women. Review of medical history then followed, using computerized pharmacy and medical record data from a large integrated health system. Results showed that among ever users of EC, adolescents were numerically more likely than young adults to cite no contraception as their reason for seeking EC, although the difference was not statistically significant (30% vs. 24%, $p = 0.38$). However,

the authors did not observe a higher prevalence of sexually transmitted infections in adolescent users. The rate of repeat EC use was essentially the same in both age groups. The only statistically significant difference in reason for seeking EC between the two age groups was due to rape/statutory rape. Specifically, rape/statutory rape were reported by 13% of adolescents compared to < 1% of young adults that ever used EC. The authors conclude that the findings reinforced the necessity of accessible EC to the adolescent population.

Meta-analyses

Four publications primarily examined contraceptive behavior following advance provision of EC.^{12-14, 74}

Raymond et al. 2007 published results from a meta-analysis to examine the population effects of increased access to EC on pregnancy rates and EC use.⁷⁴ The EC regimens examined include the Yuzpe regimen, levonorgestrel-only regimen (two 0.75 mg tablets taken 12 hours apart or as a single dose), and mifepristone. A total of 23 studies conducted in 10 countries were included in this analysis; 10 of these 23 were randomized controlled trials and four were observational studies, enrolling 13,564 women. The remaining nine studies compared population-level statistics and were non-comparative in designs. None of the included studies found clinically or statistically significant differences between intervention and control groups in pregnancy or abortion rates. The authors suggest that poor access to EC may not be the only impediment to their use since women often fail to take EC after the most risky coital acts even when EC is available. Nevertheless, the authors note that only in two of the studies^{10, 75} was access to EC not through prescription. They thus welcomed the 2006 Plan B switch action. Notably, this analysis was published shortly after Plan B became available OTC. To date, this medical officer is unaware of any comparative data to assess pregnancy rates specifically before and after the switch.

Polis et al. 2007, in another meta-analysis, assessed eight randomized controlled trials from three countries (U.S., China, and India) that included 6389 subjects.¹² EC regimens (given via advance provision) assessed in these studies include the Yuzpe regimen (two studies), levonorgestrel alone (five studies), or mifepristone (one study). Follow-up ranged from three to 12 months. All studies attempted to measure pregnancy, whereas three studies also measured sexually transmitted infections. Individual studies and pooled analysis (including pooled analysis by regimen type) did not show significance difference in pregnancy rates between advance provision and control groups. The odds ratio for levonorgestrel-only studies (advance provision group vs. control group) was 0.87, with the 95% confidence interval of 0.67 to 1.13). In addition, none of the three studies that measured STI rates found significant differences between groups (combined odds ratio 0.99, 95% confidence interval 0.73 to 1.34). EC use was significantly higher in the advance provision group; the combined odds ratio for EC use was 2.52 (95% confidence interval 1.72 to 3.70). In general, the interval between unprotected sex and EC use was shorter for women receiving EC in advance. The authors conclude that the absence of pregnancy reduction on the population level “should not impede efforts to ensure all women have access to EC when they need it.” The authors offered explanations as to possible reasons for the apparent disparity between theoretical and actual effectiveness of EC in reducing

pregnancy rate. First, more complicated EC regimens such as the Yuzpe regimen may be associated with more incorrect use and lower efficacy. Second, women may not perceive themselves to be at risk for pregnancy and may fail to use EC after unprotected sex, despite ready availability.

In a larger meta-analysis, **Polis et al. 2007 (also updated in 2010)** expanded their earlier meta-analysis to include studies conducted in Sweden. This expanded analysis was based on 11 randomized controlled trials to evaluate advance provision of EC (representing 7695 women from four countries – U.S., China, India, and Sweden).¹³ The authors found that advance provision of EC did not lead to increased rates of sexually transmitted infections (odds ratio 1.01, 95% confidence interval 0.75 to 1.37), increased frequency of unprotected intercourse (odds ratio at 6 months 0.96, 95% CI 0.79 to 1.16), or changes in contraceptive methods. Furthermore, the authors report that women who received EC in advance were equally likely to use condoms as women who received EC via standard access (odds ratio of condom use at 12 months 1.01, 95% CI 0.87 to 1.16). The authors again conclude that advance EC provision does not negatively impact sexual and reproductive health behaviors and outcomes. They state that women should have easy access to EC to decrease the chance of pregnancy.

Meyer et al. 2010 conducted a review using many of the studies included in the two **Polis et al. 2007** publications, but focused specifically on women 24 years of age or younger.¹⁴ This review included seven randomized controlled trials (evaluating advance EC provision vs. control), and represented a total of 5285 young women. Although the authors did not conduct any de novo analysis, and their conclusions are in line with those offered by **Polis et al.**

Additional review articles

Four publications are review articles. **Cheng et al. 2008** provides a summary and meta-analysis of efficacy data on all emergency contraception methods, including levonorgestrel.³² **Harper et al. 2008** and **Haynes 2007** contain no original analyses and both present a review of data contained in literature; both draw a conclusion in support of increased access to EC for adolescents.^{76, 77} In addition, a recent publication (**Raymond et al. 2011**) that assessed available data on peri-coital oral contraception (a different indication) with levonorgestrel will not be discussed here.⁷⁸

Medical officer comment:

A large body of literature is now available on the effect of expanded access to EC, mostly in the form of advance provision. These data have demonstrated that improved access to EC consistently increased its reported use; when women were provided with EC in advance of need, not only did they use EC more often, they also used EC sooner after unprotected sex. Concerns for adverse health or behavioral effects stemming from increased EC availability have not been borne out. Data reviewed here indicate that advance provision of EC did not increase rates of sexually transmitted infections, decrease condom use, encourage adoption of less reliable contraceptive methods, or otherwise negatively affect sexual and reproductive behavior. However, to date, evidence has not emerged to indicate that increased EC access reduced unintended pregnancy or abortion rates on a population level.

One possible explanation for this observation may be the different dosing regimens of Plan B and Plan B One-Step. The advance provision experience has been based entirely on the two-dose levonorgestrel regimen, in which the second dose is taken 12 hours after the first. In study #9727, the actual use study conducted to support OTC switch of Plan B (sNDA 21-045, submitted April 16, 2003), while the proportion of subjects who took the first dose of Plan B within 72 hours of unprotected intercourse was 92.4%, the proportion of subjects who took both doses correctly (first dose within 72 hours of unprotected intercourse, and the second dose at 12 hours after the first dose) dropped to 68-72% (see DNCE medical officer review dated January 12, 2004). In contrast, correct usage of Plan B One-Step, the single-dose regimen, was observed in 92.3% of the adolescent subjects. Clearly, a simpler dosing regimen is more conducive to correct usage, which may translate into better effectiveness. Thus, despite the inability to tie Plan B availability directly to any reduction in pregnancy rates, one should not presume that Plan B One-Step is destined for the same outcome. Furthermore, obtaining reliable data to show a significant reduction in pregnancy rates due to EC use would require a very large placebo-controlled, randomized trial that may not be feasible because of ethical concerns.

A second explanation for the lack of pregnancy reduction on the population level lies in the observation that many women still fail to use EC after unprotected sex has occurred, despite EC availability. As observed in Raymond 2006, more than one third of women in both increased access and standard access groups admitted to having had unprotected sex at least once without using EC treatment afterwards. Furthermore, the proportion of women reporting unprotected sex without using EC is likely to be an underestimate because of recall bias, denial, or the desire to please investigators. Since EC can only reduce the risk of pregnancy when it is actually used, it is likely that many unprotected coital acts remain “uncovered” by EC.

Despite the lack of apparent benefit in reduction of unintended pregnancy rates to date, I believe that the potential public health impact of EC should not be discounted. There is also consensus on this among the two primary medical reviewers for this supplemental application (based on personal communication with Dr. Daniel Davis, medical officer responsible for Plan B/Plan B One-Step, Division of Reproductive and Urologic Products).

9.2 Labeling Recommendations

Detailed labeling review will be conducted by reviewers in the Division of Nonprescription Regulation Development (DNRD). Given that the only change proposed in this supplemental application involves the target population, there should not be substantive revisions in the resultant new label. This medical officer has the following comment on the proposed label submitted by the sponsor:

Pertaining to the Principal Display Panel (PDP) and Drug Facts:

- Deleting “Rx only for women younger than age 17” from the PDP is appropriate. However, it would still be appropriate to state that this product is “for women only.”

- The statement on the PDP, (b) (4) is promotional in nature and is not acceptable.
- The statement on the PDP, “Reduces chance of pregnancy after unprotected sex (b) (4) (b) (4) is streamlined by deleting the qualifying portion in the parentheses. This is acceptable.
- (b) (4)
- (b) (4)
- (b) (4)
Second, (b) (4) an inadvertent association here should be avoided. In addition, it is unclear as to what the phrase (b) (4)” intends to convey. (b) (4)
- I do not see a reason to alter the original phrase “One Tablet One Dose.” (b) (4)
- The bulleted statement under “Directions” in Drug Facts directing those younger than 17 years to see a healthcare professional has been deleted. This proposed change is appropriate.
- (b) (4)

With respect to the proposed Consumer Information Leaflet:

- Under the “What Plan B One-Step is not” section, a statement is added to state that (b) (4) [redacted]” I do not recommend the inclusion of this statement for the same reason given above regarding the mechanism of action.
- In the same vein, the applicant has revised the language in the section under (b) (4) [redacted] I do not agree with this proposed change.
- An allergy alert statement is added to the section “When not to use Plan B One-Step.” This is acceptable.
- Previous language has been modified to state “(b) (4) [redacted] The previous version of this section should be retained.
- Other revisions to the Consumer Information Leaflet pertain to the sponsor’s attempt to delete redundant information. Refer to DNRD’s labeling review for additional comments.

9.3 Advisory Committee Meeting

No advisory committee meeting was held for the current supplemental application because an advisory committee meeting in 2003 addressed Rx-to-OTC issues for the closely related product, Plan B. Because the committee opinions are relevant to the current application, a summary follows:

On December 16, 2003, FDA convened a joint session of the Nonprescription Drug Advisory Committee (NDAC) and the Advisory Committee for Reproductive Health Drugs (ACRHD) to discuss NDA 21-045, which sought OTC marketing of Plan B.⁸²

After reviewing the data submitted to support of full OTC availability, the joint Committee voted overwhelmingly in favor of the Rx-to-OTC switch of Plan B without age restriction. Questions posed to the Committee and the vote tallies were the following:

Question 1. Does the Actual Use Study (AUS) demonstrate that consumers used the product as recommended in the proposed labeling?

Yes = 27; No = 1; Abstain: 0

Question 2. Are the AUS data generalizable to the overall population of potential non-Rx users of Plan B?

Yes = 27; No = 1; Abstain: 0

Question 3. Based on the AUS and literature review, is there evidence that non-Rx availability of Plan B leads to substitution of emergency contraception (EC) for the regular use of other methods of contraception?

Yes = 0; No = 28; Abstain: 0

Question 4. Do the data demonstrate that Plan B is safe for use in the non-prescription setting?

Yes = 28; No = 0; Abstain: 0

Question 5. Are the plans for introduction of Plan B into the non-Rx setting adequate with respect to consumer access and safe use? If no, what other options would you recommend?

Yes = 22; No = 5; Abstain: 1

Question 6. Do you recommend Plan B be switched from Rx to non-Rx status?

Yes = 23; No = 4; Abstain: 0; (one member left before voting commenced)

Medical officer comment:

*Based on my review of the meeting transcript, there was one aspect of the Committee's deliberation that is pertinent to this supplemental application. Committee members who supported the OTC status switch by voting yes for question 6 endorsed the switch as proposed with respect to the age of target population. Furthermore, while most saw no need for any postmarketing studies, some members recommended **post-approval** studies in adolescents to assess their comprehension and contraceptive behavior since they supported approval with no age restriction. Data contained in this supplemental application serve as validation that the original dual marketing status action was unnecessary.*

Given that Plan B One-Step involves a simpler dosing regimen than Plan B, recommendations made by the 2003 Committee for OTC marketing apply to Plan B One-Step. Data contained in this application and in updated literature review have not presented evidence to contradict what was presented to the 2003 Advisory Committee. In fact, information collected from postmarketing surveillance and literature since 2003 have strengthened the case for decreasing barriers to access for adolescents. Convening another Advisory Committee meeting is therefore unnecessary for this supplemental application.

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Clinical Review

Christina Chang, M.D., M.P.H.

NDA 21-998 Efficacy Supplement

Plan B One-Step (Levonorgestrel 1.5 mg)

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Clinical Review

Christina Chang, M.D., M.P.H.

NDA 21-998 Efficacy Supplement

Plan B One-Step (Levonorgestrel 1.5 mg)

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Clinical Review

Christina Chang, M.D., M.P.H.

NDA 21-998 Efficacy Supplement

Plan B One-Step (Levonorgestrel 1.5 mg)

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/s/

CHRISTINA Y CHANG
10/05/2011

LESLEYANNE A FURLONG
10/05/2011

I concur with Dr. Chang's review and recommendations.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:				been established.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	Not applicable.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	Not applicable. This product is indicated for emergency contraception and is not intended to be taken chronically.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			MedDRA
24.	Has the applicant adequately evaluated the safety issues that			X	

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	are known to occur with the drugs in the class to which the new drug belongs?				
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			For actual use study, DR-LEV-302
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?	X			The submission includes required label comprehension study and actual use study.
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?		X		Still need sponsor's assessment; see reviewer comments below
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			The safety database is accessible and analyzable, using JMP application.
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	Not applicable.
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	IRB and with adequate informed consent procedures?				

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___YES___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Reviewer comments:

1. An Information Request was sent to the applicant on February 24, 2011 to request additional safety data. A follow-up teleconference was held between the DNCE clinical review team and the applicant on February 28, 2011 to discuss clarifications on request. There were also email communications between the Agency and Teva on March 2 and 3, 2011 for additional clarification of the request. The applicant committed to provide the following information as soon as possible and during the review cycle:
 - Narrative summary and analysis of postmarketing safety information for marketed levonorgestrel emergency contraception products from FDA’s Adverse Event Reporting System (AERS) and the World Health Organization’s (WHO) International Drug Monitoring Program since July 10, 2009. Data should be stratified based on age, race/ethnic group, drug-drug interactions, and drug-disease interactions if feasible.
 - An assessment of potential abuse of levonorgestrel used as emergency contraception.
 - OTC distribution data as well as prescription use data since July 10, 2009.
 - An assessment of safety based on the totality of postmarketing contained in the three databases (AERS, WHO, and Teva’s own pharmacovigilance database) on whether they present a consistent safety profile for levonorgestrel.

The applicant was informed that if the above information was submitted within the last three months of the review cycle, it may be considered a major amendment, which would extend the review clock.

2. The applicant’s request for priority review should be denied, because this efficacy supplement is not submitted in response to FDA’s Written Request.

3. In an email communication dated March 29, 2011, Teva confirmed that distribution information will be provided to FDA by April 1, 2011, and that additional postmarketing data analysis based on AERS and WHO databases will be provided to FDA by April 8, 2011.

4. The requested distribution information for Plan B and Plan B One-Step was submitted in an amendment dated March 31, 2011.

5. The requested AERS and WHO analyses were provided in a submission dated April 6, 2011.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

6. In an email communication dated March 30, 2011, Teva also committed to providing an assessment of abuse potential of Plan B One-Step.
7. Teva should provide, as soon as possible, safety information for the 12 subjects who had used Plan B One-Step but had not completed all three follow-up contacts by DR-LEV-302 study report date.

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/s/

CHRISTINA Y CHANG
04/08/2011

LESLEYANNE A FURLONG
04/08/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021998/S-002

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/ Serial Number: 21998/S002

Drug Name: Plan B One-Step (Levonorgestrel 1.5 mg)

Indication(s): Emergency Contraception

Applicant: DURAMED PHARMACEUTICALS INC

Date(s): **Correspondence date:** February 7, 2011
Document ID: NDA Review Date: July 22, 2011
PDUFA Goal Date: December 10, 2011

Review Priority: Standard

Biometrics Division: DB4

Statistical Reviewer: Rima Izem

Concurring Reviewers: Yan Wang

Medical Division: DNCE

Clinical Team: Christina Chang (Clinical Reviewer)
Oluwamurewa Oguntimein (Social Scientist)
Lesley-Anne Furlong (Team leader)

Project Manager: Melissa Furness

Keywords:
Actual Use Study, Label Comprehension Study

Memorandum to file

This memorandum is the statistical review for the label comprehension study (LCS) and the actual use study (AUS). The review will focus on the data structure of the findings and give a brief background and summary of findings. We refer to the social scientist's review for more details on design and exploratory results for the label comprehension study. We refer to the clinical review for more details on the design of the actual use study and applicant's results.

Background

Plan B and Plan B One-Step are levonorgestrel products for emergency contraception that differ mainly in the dosing regimen. Use of Plan B involves taking two tablets 12 hours apart, whereas use of Plan B One-Step involves taking a single tablet. Plan B was first approved for prescription use in 1999, and then approved for both prescription and over-the-counter (OTC) use in 2006. Females 18 or older could have access to the drug OTC, whereas females younger than 18 could only have access to the drug by prescription. In 2009, OTC access for Plan B was approved for females 17 and older.

Plan B One-Step also received dual approval for prescription and OTC use in 2009. However, the cut-off date for availability in OTC was 17 years of age instead of 18 years of age. Thus, females 17 or older have access to Plan B One-Step OTC, whereas females younger than 17 have access to the drug by prescription.

This supplemental NDA seeks to expand the OTC population to include all females of reproductive age by changing the marketing status to OTC for those females less than 17 years of age. This expansion of the availability of the drug was not granted by CDER after review of a previous NDA submission for Plan B (NDA 21-045/S-011). The main deficiency identified by CDER was the insufficient number of adolescents in the original Label Comprehension (LCS) and Actual Use Study (AUS).

New consumer studies were conducted by the applicant in adolescents of 16 years or younger to address the deficiency identified by CDER. This NDA dossier has results from an LCS (DR-LEV-301), enrolling 335 subjects 12 – 17 years of age, and an AUS (DR-LEV-302), enrolling 343 subjects 11 – 17 years of age.

Label Comprehension Study

The label comprehension study is open-label, non-comparative, multi-center study. The goal of the study is to insure that subjects understand the instructions from the label.

A list of 6 concepts was identified by applicant and divided into 3 primary objectives and 3 secondary objectives. To test these objectives a 19- item questionnaire was developed with each question or item testing one objective. To demonstrate understanding of a concept, subjects were to provide a correct response on all or most of the questions testing this concept.

Data source

The data for this study was not originally submitted by the applicant. An information request was sent to the applicant on May 18th, 2011 to submit the data. In June 21st, 2011 the applicant submitted the data to FDA in the m1 folder at
\\Cdsesub1\evsprod\NDA021998\0060\m1\us\114-label\1141-draft-label\drlev301.xpt

The dataset has 222 variables. These variables include each subject's answers to eligibility questions, demographic information as well as answers to the LCS questions. There are also many derived variables. We found the most important derived variables to be the following

- the primary and secondary objectives (metobj1, metobj2, metobj3, metobj4, metobj5, metobj6) derived from questionnaires' answers
- eligibility indicator variable (eligpop) derived from eligibility questions
- primary population indicator variable (pripop) derived from the location of centers and excluding the data from Miami and Chicago due to irregularities at those sites

Reviewer's comment: *The dataset did not use the electronic data formatting principles outlined in CDISC standards. For example, instead of coding the subject's response to questions according to the question number in a vertical format, the applicant coded the answers to each question separately in a column in a horizontal format. Although the documentation provided the definition of each of the 222 variables in the dataset, the documentation did not outline which of these variables were used in the primary analysis. Our comments above on most important derived variables in the primary analysis reflects our best guess, from the statistical analysis plan and the variable documentation, on which variables were used among the 222 variables provided.*

Results

Table 1 shows the results for each communication objective. The rate of correct understanding exceeds 85% for all but the second key concept. A possible explanation

for this low rate may be due to ambiguous phrasing of a question as suggested in the applicant's dossier and confirmed in the social scientist's review.

Table 1: Main Findings from Label Comprehension Study

Key Concepts	Number of Questions asked	Correct responses needed to demonstrate understanding of key concepts	Proportion of subjects with correct understanding	
			n/N (%)	95% CI using exact method
Primary Objectives				
1. Plan B is indicated for prevention of pregnancy after unprotected sex	4	3	300/335 (89%)	(86%, 93%)
2. Plan B should be taken as soon as possible after sex	4	3	277/335 (83%)	(78%, 87%)
3. Plan B does not prevent sexually transmitted diseases or HIV/AIDS	2	2	310/335 (92%)	(89%, 95%)
Secondary objectives				
4. Plan B should not be used in place of regular contraception	3	2	309/335 (92%)	(89%, 95%)
5. Plan B should be taken within 72 hours after sex	3	2	319/335 (95%)	(92%, 97%)
6. Plan B should not be used by women who are already pregnant	3	2	320/335 (95%)	(93%, 97%)

Reviewer's comment: We reproduced the applicant's findings from the provided dataset. Note that no thresholds for win criteria were pre-specified before unblinding of the data.

Thus, these comprehension rates and their confidence interval are provided as a descriptive summary of the data.

Actual Use Study

The AUS is open-label, non-comparative, single-use multi-center study.

The goals of the study are the following:

- 1) Determine whether adolescents can appropriately self-select to take Plan B One-Step without provider counseling
- 2) Determine whether adolescents can correctly use Plan B One-Step based on directions in the label

Data source

The AUS data and documentation is at the following link

<\\Cdsub1\evsprod\NDA021998\0053\m5\datasets\dr-lev-302\analysis\datasets>

The AUS data originally submitted with the NDA in February 7th, 2011 did not match the “define.pdf” documentation file. An information request was sent to the applicant in March 30th, 2011 and the applicant submitted the new dataset with modified documentation in April 7th, 2011.

The dataset has a total of 355 variables or columns including both *raw data* (or answers to questions or information on adverse events) and also many variables derived from these raw data (such as screening, enrollment, eligibility, appropriate self selection, whether product was provided, and correct use). We found the most relevant derived variables to work with to be the following:

- *enrll*: indicator of whether the subject enrolled in the study
- *incsel*: indicator for incorrect self selection or *corrself*: indicator for correct self selection
- *dispens1*: indicator for whether the product was dispensed
- *corrusep*: indicator for whether the product was correctly used

Reviewer’s comment: *As for the LCS dataset, the AUS dataset did not use the electronic dataset principles outlined in CDISC standards. The data documentation did not outline which variables were used for each primary endpoint. The above comment on most relevant derived variable reflects our best guess, from the statistical analysis plan and the documentation provided, on which variable was used in the primary analyses.*

Primary endpoint

Our review reproduced the applicant’s findings for the primary endpoints. There were two primary endpoints,

- The proportion of enrolled subjects at the screening visit who appropriately self-selected. Results: **309/343 (90.1%)** with 95% CI **(86.4% - 93.0%)**
- Proportion of subjects who appropriately used the product from those who correctly self selected and been given the product. Results: **263/297 (88.5%)** with 95% CI **(84.3% - 92.0%)**

Reviewer's comments: No threshold for success was pre-specified for the overall adolescent population or for age cohorts. Therefore, we leave it to the clinical reviewer to comment on the adequacy of these results.

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/s/

RIMA IZEM
10/12/2011

YAN WANG
10/12/2011
I concur.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 21998

**Applicant: Teva Branded
Pharmaceutical Products R&D, Inc**

Stamp Date: 02/07/2011

Drug Name: Plan B- one step NDA Type: standard

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)			X	This is self selection and actual use study reports
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

The name of variables in the original dataset (pop.xpt) sent by the applicant does not match the names of the variables in the define.pdf. There are over 2090 variables in that dataset. Thus, the following comment was sent to sponsor on 03/30/11

"We are having difficulty conducting our statistical review of the dataset (pop.xpt) and documentation (define.pdf) you submitted. Please submit either the dataset corresponding to the documentation or the documentation corresponding to the dataset before the filing date (April 8, 2011). We note that the names of the variables in the dataset you submitted do not match the names of the variables in the define.pdf file. This makes deriving the primary endpoints problematic. In general, we ask applicants to submit datasets including (a) "raw" variables corresponding to all variables collected on subjects in the study and (b) derived variables corresponding to variables derived from the raw variables and needed for the statistical analyses. Proper documentation should be submitted to allow us to check the statistical analyses on the derived variables as well as check the derivation from raw to derived variable. "

The applicant sent in a new dataset on 04/05/2011 corresponding to the define.pdf file.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.			X	This is a safety data, not efficacy data for a claim
Endpoints and methods of analysis are specified in the	X			

File name: Statistics Filing Checklist for NDA 21998

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

protocols/statistical analysis plans.				
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.		X		Assessing missingness was not part of the statistical analysis plan

Brief summary of controlled clinical trials

The following table contains information on the relevant trials contained in the submission.

Study number	Design	Treatment arms/Sample size	Primary endpoint/Analysis	Sponsor's findings
302	Multicenter, one arm, open label study. Multiple - age cohort and combined self selection and actual use study	Plan B one Step	Primary endpoints: (1) Percent of enrolled subjects at the screening visit who appropriately self-selected. (2) Percent of subjects who appropriately used the product from those who correctly self selected and been given the product. Secondary endpoint: Percent of subjects who reported repeat use of EC.	Estimate n/N (%) and 95% CI (1) 309/343 (90.1%) (86.4% - 93.0%) (2) 263/297 (88.5%) (84.3%-92.0%)

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Background:

The following are the regulatory milestones of this product and the motivation to the current supplement.

Plan B® brand of emergency contraceptive pills, distributed by Teva Women's Health, Inc. (formerly Duramed Pharmaceuticals, Inc.) is indicated for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure (NDA #21-045). The Plan B® regimen consists of one dose of levonorgestrel 0.75 mg taken as soon as possible within 72 hours after unprotected sex, followed by a second identical dose 12 hours later.

Plan B® was approved by FDA on July 28, 1999 for marketing as a prescription product. A request to switch the product from prescription (Rx) to over-the-counter (OTC) status, based on label comprehension and actual use studies, resulted in an approval for OTC sale to consumers aged 18 years and older on August 24, 2006, while maintaining the prescription requirement for women age 17 and younger.

Subsequently Duramed Research, Inc. (now Teva Women's Health Research) submitted an NDA (NDA #21-998) for Levonorgestrel 1.5 (for study purposes referred to as Plan B® 1.5), an emergency contraceptive pill regimen consisting of a single dose of 1.5 mg levonorgestrel to be taken within 72 hours of unprotected intercourse. On July 10, 2009, the FDA approved this NDA with the trade name of Plan B One-Step®, by prescription for women younger than 17 years old and over the counter for consumers 17 years and older.

FDA indicated that to allow for full OTC access, additional information was needed demonstrating that young women aged 17 years and younger understand the key concepts needed for safe and effective use.

Rima Izem	04-05-2011
_____ Reviewing Statistician	_____ Date
Yan Wang	04-05-2011
_____ Supervisor/Team Leader	_____ Date

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/s/

RIMA IZEM
04/18/2011

YAN WANG
04/18/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021998/S-002

OTHER REVIEW(S)

Labeling Review for Plan B One-Step (levonorgestrel) Tablet, 1.5 mg *Draft Labeling*

SUBMISSION DATES: April 15, 2013

NDA/SUBMISSION TYPE: 021998/S-002/Class 2 resubmission

ACTIVE INGREDIENTS: Levonorgestrel, 1.5 mg

DOSAGE FORM: Tablet

SPONSOR: Teva Branded Pharmaceutical Products, R&D, Inc.
41 Moores Rd., P.O. Box 4011
Frazer, PA 19355

Contact: Amy C. Hummel, MS
Associate Director, Regulatory Affairs
Telephone: (610) 727-6322/ Fax: (215) 293-74-39
Email: amy.hummel@tevapharm.com

REVIEWER: Maria Ysern, MSc, DNRD, ODE IV

TEAM LEADER: Ruth E. Scroggs, PharmD, RPh, DNRD, ODE IV

PROJECT MANAGER: Doris J. Bates, PhD., Senior Regulatory Project Manager,
DNCE, ODE IV

I. BACKGROUND

This is a review of Teva Women's Health (Teva) proposed labeling submitted on April 15, 2013, containing the revisions made and agreed upon during our April 10, 2013 teleconference with the firm. The purpose of the April 10, 2013 teleconference was to discuss labeling comments communicated to the firm in an FDA April 9, 2013 information request.

This labeling review amends our April 09, 2013 labeling review. The revised proposed labeling submitted on April 15, 2013 is listed in the following table.

Submitted Labeling
Outer Carton Label, Retail
Outer Carton Label, Clinic
Clamshell Label – Front and Back (Product Identification) Card

We compare the proposed retail carton label and proposed clinic carton label submitted on April 15, 2013, to the proposed retail carton label and proposed clinic carton label submitted on March 09, 2012, and reviewed on September 06, 2012. We compare the proposed clamshell label submitted on April 15, 2013, to the proposed clamshell label submitted on April 04, 2013, and reviewed on April 09, 2013.

II. REVIEWER'S COMMENTS

A. Retail Carton and Clinic Carton:

i. Outer Carton Label Outside Drug Facts

The promotional statement located in the principal display panel's upper left corner, is revised from [REDACTED] (b) (4) to "For age 15 and older".

Comment: This is acceptable.

ii. Outer Carton Drug Facts Label

General: The drug facts label is located on the carton's back panel.

a. Directions

The first two bulleted statements in the *Directions* section are revised as follows:

1. The proposed first bulleted statement, which addresses the consumer who is under 15 years of age, is moved in bullet order to become the second bulleted statement. It is revised from "[bullet] [REDACTED] (b) (4) [REDACTED]" to "[bullet] women under 15 years of age: talk to a doctor".

Comment: this is acceptable.

2. The proposed second bulleted statement is moved to become the first bulleted statement and adds who the intended consumer for product use is. It is revised from "[REDACTED] (b) (4) [REDACTED]" to "women 15 years of age and older: take as soon as possible within 72 hours (3 days) after unprotected sex. The sooner you take it the better it will work."

Comments: this is acceptable.

b. Other Item for Discussion: Drug Facts Format Specifications

The proposed drug facts label meets the font and format specifications as set forth under 21 CFR 201.66.

Comments: this is acceptable.

B. Clamshell Labeling – Front and Back (Product Identification) Card

A second proposed promotional statement, “Now available Over the Counter” is inserted below the previously proposed “New!” flag located in the clamshell card’s front upper right corner.

Comment: This is acceptable. Please remind the firm to remove these two promotional statements from the labeling after 6 months of marketing.

III. RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted NDA 21-998/S-002, Plan B One-Step (levonorgestrel) Tablet, 1.5 mg labeling and request final printed labeling. Request that the sponsor submit final printed labeling (FPL) identical to: immediate container label (1-count blister) submitted on October 21, 2011, outer carton (retail) label, outer carton (clinic) label, and clamshell label front and back card (Product identification cards) submitted on April 15, 2013, and the consumer information leaflet submitted on December 07, 2011.

In the approval letter, please remind the firm to remove the “New! Now available Over the Counter” promotional statements from the clamshell card’s front upper right corner after six months of marketing.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted on April 15, 2013, and evaluated in this labeling review:

Outer Carton Label, Retail
Outer Carton Label, Clinic
Clamshell Label – Front and Back (Product Identification) Card

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/s/

MARIA E YSERN
04/30/2013

COLLEEN K ROGERS
04/30/2013
signing for Ruth E. Scroggs

Labeling Review for Plan B One-Step (levonorgestrel) tablet, 1.5mg *Draft Labeling*

SUBMISSION DATES: April 04, 2013

NDA/SUBMISSION TYPE: 021998/S-002/class 2 resubmission

ACTIVE INGREDIENTS: Levonorgestrel, 1.5 mg

DOSAGE FORM: Tablet

SPONSOR: Teva Branded Pharmaceutical Products, R&D, Inc.
41 Moores Rd., P.O. Box 4011
Frazer, PA 19355

Contact: Amy C. Hummel, MS
Associate Director, Regulatory Affairs
Telephone: (610) 727-6322 / Fax: (215) 293-7439
Email: amy.hummel@tevapharm.com

REVIEWER: Maria Ysern, MSc, DNRD, ODE IV

TEAM LEADER: Ruth E Scroggs, PharmD, RPh, DNRD, ODE IV

PROJECT MANAGER Doris J. Bates, Ph.D., Senior Regulatory Project Manager,
DNCE, ODE IV

I. BACKGROUND

This review is of Teva Women's Health (Teva) labeling submitted on April 4, 2013, in response to our March 27, 2013 information request regarding NDA 21998/S-002. The firm's cover letter confirms that there are no changes to the immediate container label (1-count blister) submitted on October 21, 2011, the outer carton (retail/trade) label submitted on March 09, 2012, the outer carton (clinic) label submitted on March 09, 2012, and the consumer information leaflet submitted on December 07, 2011. However, the firm stated that the packaging tray label is no longer required due to the addition of the plastic clamshell outer packaging (discussed later in this review). The cover letter also describes the subject of this review, the submitted proposed product identification card (a front and back card label), to be inserted into the clamshell.

This review amends our September 06, 2012 review.

II. REVIEWER'S COMMENTS

Clamshell Labeling – Front and Back (Product Identification Cards)

The sponsor submitted clamshell labeling, reviewed here, in response to our March 27, 2013 information request.

The card's (front and back) color scheme is identical to the trade carton's color scheme. The proposed clear plastic clamshell package contains the proposed card. Based on a submitted packaging illustration and the firm's description in the cover letter, the proposed card itself has a central cut-out area, into which the proposed carton is inserted. The proposed carton's primary display panel label and the proposed carton's back panel label are fully visible.

We describe the proposed text and card layout as follows:

Card Front: The tradename "Plan B One-Step" and logo swirl are placed in the card's front top left corner. A "NEW!" flag appears in the card's front top right corner.

Card Back: Identical to the front, the tradename and logo swirl are placed in the card's back top left corner. The top right corner shows the following proposed Use statement "Reduces chance of pregnancy after unprotected sex".

Comment: The only item on the proposed card labeling that is not acceptable is the "NEW!" statement. Usually, when a "new" flag promoting a product is proposed, the product's new flag labeling should also include what aspect of the product is new. However, description of the product's type of newness may be confusing to the consumer. Therefore, we recommend that the sponsor remove the text "New!" from the front side of the clamshell. This change was requested in an April 9, 2013 information request letter.

III. RECOMMENDATIONS

The following recommendation was communicated to the sponsor on April 9, 2013:

Remove the text on the front side of the clamshell that reads "New!".

IV. SUBMITTED LABELING

The clamshell card front label (product identification card) and clamshell card back label evaluated in this labeling review are attached.

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/s/

MARIA E YSERN
04/09/2013

RUTH E SCROGGS
04/09/2013

Labeling Review for Plan B One-Step (levonorgestrel) tablet, 1.5mg *Draft Labeling*

SUBMISSION DATES: March 9, 2012
RELATED SUBMISSIONS: February 7, 2011
October 21, 2011
November 4, 2011
November 15, 2011
December 7, 2011
NDA/SUBMISSION TYPE: 021998/S-002/class 2 resubmission

ACTIVE INGREDIENTS: Levonorgestrel, 1.5 mg

DOSAGE FORM: Tablet

SPONSOR: Teva Branded Pharmaceutical Products, R&D, Inc.
41 Moores Rd., P.O. Box 4011
Frazer, PA 19355

Contact: Amy C. Hummel, MS
Senior Manager, Regulatory Affairs
Telephone: (610) 727-6322 / Fax: (215) 293-7439
Email: amy.hummel@tevapharm.com

REVIEWER: Maria Ysern, MSc, DNRD, ODE IV

TEAM LEADER: Ruth E Scroggs, PharmD, RPh, DNRD, ODE IV

PROJECT MANAGER Melissa H Furness, Chief, Project Management Staff, DNCE,
ODE IV

I. BACKGROUND

NDA 21-998 for Plan B One-Step (levonorgestrel) tablet, 1.5 mg, approved July 10, 2009, is an emergency contraceptive indicated for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. Plan B One-Step is available only by prescription for women younger than age 17 years and available over-the-counter for women 17 years and older.

Prior Approval supplement-002, submitted by Teva Women's Health, Inc. on February 7, 2011, proposed removing the prescription legend and switching to full OTC marketing status. However, the Agency issued a December 7, 2011 complete response letter to the firm indicating

that the supplement could not be approved and was deficient because the Secretary of Health and Human Services had concluded that the data “submitted for this product are inadequate to support approval in that they do not establish that prescription dispensing requirements should be eliminated for all ages.”

A December 7, 2011 submission included a revised consumer information leaflet (CIL) based on FDA request. The firm indicates that the December 7, 2012 CIL remains as the currently proposed CIL, therefore, our assessment of that submission is part of this document.

The March 9, 2012 resubmission by the firm addresses the deficiency listed in the February 7, 2011 complete response letter by amending their application. This submission provides to restrict the sale of Plan B One-Step as an OTC-only drug product to consumers age 15 and older. The firm’s cover letter outlines their proposed plan, which includes description of their proposed distribution restrictions and control measures.

A May 2, 2012 submission, a general correspondence, notifies the FDA of an administrative change of regulatory point of contact and firm address. Thus, this review includes the new point of contact and the new firm address.

The following labeling was submitted:

Submitted Labeling	Representative of Following SKUs	Date Submitted
Consumer Information Leaflet	used for both trade/retail and clinic	December 7, 2011
Outer Carton label, Retail/Trade	none	March 9, 2012
Outer Carton label, Clinic	none	March 9, 2012

II. REVIEWER'S COMMENTS

This review follows three previous labeling reviews, dated September 29, October 27, and November 16, 2011, respectively.

The labeling submitted December 7, 2011 and March 9, 2012, is compared to the labeling submitted November 4, November 15, 2011 and reviewed November 16, 2011.

To address the deficiency communicated in the complete response letter, the sponsor submitted the following labeling changes.

A. Retail (Trade) Carton and Clinic Carton

i. Outer Carton Label Outside Drug Facts

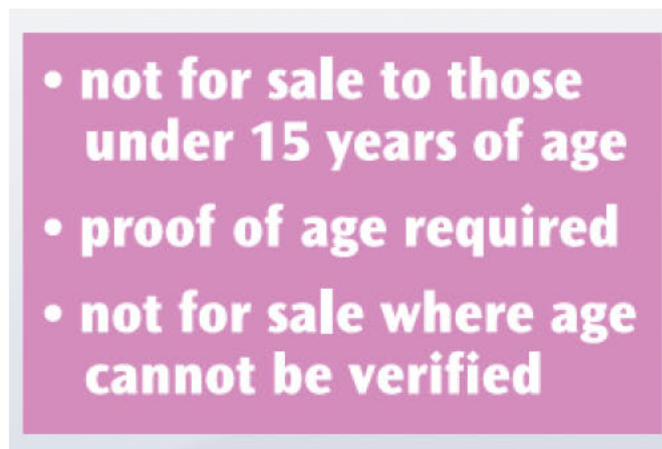
- a. In the PDP’s upper left corner, the originally proposed statement, (b) (4) (b) (4) ” is revised to the following statement:

(b) (4)

Comment:

(b) (4)

- b. In the back panel's lower left corner, beside the Drug Facts box, a new box with three lines of text is added. The image showing 3 lines of white text on pink background appears below:



Comment: *The first line of added text directly states the 15 years age restriction and the second and third lines inform the consumer of the controls used to verify the consumer's age. Such a set of statements are modeled after that of nicotine-containing smoking cessation products, which are OTC drug products that are restricted for sale to consumers of a certain age (18 and older for nicotine-containing products). The prominence and location of these three statements are neither in conflict with required general labeling provisions nor with labeling requirements for OTC drug products.^{1,2} Therefore, these statements are generally acceptable. However, comment on the acceptability of the 15 year restriction and set of controls is beyond the scope of this labeling review.*

ii. **Outer Carton Drug Facts Label**

a. *Directions*

A new first bullet is inserted that reads:

¹ 21 CFR Part 201 Labeling, Subpart A –General Labeling Provisions

² 21 CFR Part 201 Labeling, Subpart C -- Labeling Requirements for Over-the-Counter Drugs

“[bullet] (b) (4)”

Comment: *The bullet instructs an under 15 year old who is restricted from purchasing the drug product to ask a doctor before using it. The format and location of this bullet under Directions is acceptable in accordance to 21 CFR 201.66(c)(6). However, comment on the acceptability of the 15 year restriction is beyond the scope of this labeling review.*

iii. Immediate Container Label (1-count blister)

There are no changes to the immediate container label submitted October 21, 2011 and reviewed November 16, 2011. No immediate container label is submitted.

Comment: *If an approval letter is issued, it should request that the sponsor submit this label as part of the final printed labeling (FPL) for this supplement in order to maintain a record of the complete labeling that may be approved as part of this supplement.*

iv. Consumer Information Leaflet

The consumer information leaflet (CIL) is unchanged from the CIL submitted December 7, 2011, which is consistent with the CIL submitted November 15, 2011 except for the addition of the following requested language:

- If you are sexually active, you should see a healthcare provider for routine checkups. Your healthcare provider will talk to you about and, if necessary, test you for sexually transmitted diseases, teach you about effective methods of routine birth control, and answer any other questions you may have.

The CIL is not submitted. The sponsor states that the leaflet is not accessible to the consumer until the product has been purchased and opened. The information regarding the conditions for sale is provided on the outside carton.

Comment: *This is acceptable; however, if an approval letter is issued, it should request that the sponsor submit this label as part of the FPL for this supplement in order to maintain a record of the complete labeling that may be approved as part of this supplement.*

v. Packaging Tray (Retail)

The retail packaging tray submitted November 4, 2011 was found acceptable in the November 16, 2011 labeling review, therefore, no packaging tray label is submitted.

Comment: *This is acceptable; however, if an approval letter is issued, it should request that the sponsor submit this label as part of the FPL for this supplement in*

order to maintain a record of the complete labeling that may be approved as part of this supplement.

III. RECOMMENDATIONS

Issue an APROVAL letter to the sponsor for the submitted NDA 21-998/S-002, Plan B One-Step (levonorgestrel) tablet, 1.5 mg and request final printed labeling. Request the sponsor to submit final printed labeling (FPL) identical to: immediate container label (1-count blister) submitted on October 21, 2011, outer carton (retail/trade) label and outer carton (clinic) label submitted on March 09, 2012, packing tray submitted November 4, 2011, and consumer information leaflet submitted December 7, 2011.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

3 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MARIA E YSERN
09/06/2012

RUTH E SCROGGS
09/06/2012

Labeling Review for Plan B One-Step (levonorgestrel) tablet, 1.5mg *Draft Labeling*

SUBMISSION DATES: November 4, 2011
November 15, 2011

RELATED SUBMISSIONS: February 7, 2011
October 21, 2011
October 27, 2011 (e-mail)

NDA/SUBMISSION TYPE: NDA 21-998/ S-002

ACTIVE INGREDIENTS: Levonorgestrel, 1.5 mg

DOSAGE FORM: Tablet

SPONSOR: TEVA/Teva Women's Health
415 Privet Road, P.O. Box 1005, PA 19044-8005
Phone 215-293-6200
Contact: Valerie M. Mulligan, Senior Director, Regulatory Affairs

REVIEWER: Maria Ysem, IDS, DNRD, ODEIV

TEAM LEADER: Colleen Rogers, PhD, DNRD, ODE IV

PROJECT MANAGER Melissa H. Furness, Chief Project Manager, DNCE, ODE IV

I. BACKGROUND

This is the third labeling review of this supplement (see also labeling reviews dated Sept 29 and Oct 27, 2011). This submission provides the responses to Labeling Comments sent to the Sponsor by the Agency on Nov 01, 2011. In the Nov 1, 2011 labeling comments, FDA requested that the sponsor remove the claim (b) (4)

(b) (4) In general, we do not think that physician recommended promotional labeling claims are appropriate for nonprescription products. Furthermore, the study that was submitted to support this claim was performed with Plan B One-Step available in its dual marketing status (as both a prescription and OTC product); thus, the study's relevance to Plan B One-Step marketed solely as a nonprescription product is unknown. Teva Women's Health, Inc., has accepted the revision proposed by the Agency to remove the claim (b) (4) (b) (4) all pieces of their proposed drug product labeling.

Submitted Labeling	Date Submitted	Representative of the Following SKUs
Trade (Retail) Carton label	Nov 4, 2011	n/a
Clinic Carton label	Nov 15, 2011	n/a
Consumer Information Leaflet	Nov 15, 2011	n/a
Packaging tray	Nov 4, 2011	n/a

The submitted labeling was compared to the draft labeling submitted October 21, 2011 and the currently approved labeling, dated July 10, 2009, that was approved as part of the original NDA submission.

II. REVIEWER'S COMMENTS

A. Retail (Trade) Carton

i. Carton Label Outside Drug Facts

The statement [REDACTED] (b) (4) has been removed from the PDP as requested by the Agency. *This is acceptable.*

ii. Carton Drug Facts Label

a. No changes to the Carton Drug Facts label. *This is acceptable.*

b. The Drug Facts font and format specifications meet the requirements of 21 CFR 201.66(d). *This is acceptable.*

iii. Consumer Information Leaflet

a. The statement [REDACTED] (b) (4) has been removed from the front panel of the Consumer Information Leaflet (CIL) as requested by the Agency. *This is acceptable.*

b. The layout of the text has been modified so that all instances of the product name Plan B One-Step appear on the same line of text, and not broken across lines. *This is acceptable.*

c. The layout of the CIL has been modified from a 2-sided leaflet to a single-sided leaflet that is 12x4 inches, but continues to fold down to 2x2 inches. This change is for compatibility with the packaging machine. *This is acceptable.*

B. Clinic Carton

i. Carton Label Outside Drug Facts

The statement [REDACTED] (b) (4) has been removed from the PDP as requested by the Agency. *This is acceptable.*

ii. Carton Drugs Fact Label

a. No changes to the Carton Drug Facts label. *This is acceptable.*

b. The Drug Facts font and format specifications meet the requirements of 21 CFR 201.66(d). *This is acceptable.*

iii. Consumer Information Leaflet

Note: the same consumer information leaflet is used for both the retail and clinic cartons.

a. The statement [REDACTED]^{(b) (4)} has been removed from the front panel of the Consumer Information Leaflet (CIL) as requested by the Agency. *This is acceptable.*

b. The layout of the text has been modified so that all instances of the product name Plan B One-Step appear on the same line of text, and not broken across lines. *This is acceptable.*

c. The layout of the CIL has been modified from a 2-sided leaflet to a single-sided leaflet that is 12x4 inches, but continues to fold down to 2x2 inches. This change is for compatibility with the packaging machine. *This is acceptable*

C. Packaging Tray

The claim [REDACTED]^{(b) (4)} (with underlying caduceus image) has been removed from the front panel of the Packaging Tray as requested. *This is acceptable.*

III. RECOMMENDATIONS

Issue an APPROVAL letter to the sponsor for the submitted NDA 21-998/ S-002 for Plan B One-Step (levonorgestrel) tablet, 1.5 mg and request final printed labeling. Request that the sponsor submit final printed labeling (FPL) identical to: 1-count immediate container (blister) label submitted October 21, 2011, retail (trade) carton label and packaging tray submitted November 4, 2011, and clinic carton label and single-sided consumer information leaflet submitted November 15, 2011.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

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/s/

MARIA E YSERN
11/16/2011

COLLEEN K ROGERS
11/16/2011

Labeling Review for Plan B One-Step (levonorgestrel) tablet, 1.5mg *Draft Labeling*

SUBMISSION DATES: October 21, 2011
October 27, 2011 (e-mail)

RELATED SUBMISSIONS: February 7, 2011

NDA/SUBMISSION TYPE: NDA 21-998/ S-002

ACTIVE INGREDIENTS: Levonorgestrel, 1.5 mg

DOSAGE FORM: Tablet

SPONSOR: TEVA/Teva Women's Health
415 Privet Road, P.O. Box 1005, PA 19044-8005
Phone 215-293-6200
Contact: Valerie M. Mulligan, Senior Director, Regulatory Affairs

REVIEWER: Maria Ysern, IDS, DNRD, ODEIV

TEAM LEADER: Colleen Rogers, PhD, DNRD, ODE IV

PROJECT MANAGER Melissa H. Furness, Chief Project Manager, DNCE, ODE IV

I. BACKGROUND

This submission provides the responses to Labeling Comments sent to the Sponsor by the Agency on September 30, 2011. Teva Women's Health, Inc., has accepted the majority of the Division's comments on the proposed cartons and consumer information leaflet. The sponsor has also provided additional pieces of labeling. On October 27, 2011 the sponsor confirmed by e-mail that the trade (retail) carton label serves as a representative label for the clinic carton label. An official submission of this confirmation is forthcoming.

Submitted Labeling	Representative of Following SKUs
Retail (Trade) Carton label	Representative of Clinic carton
Consumer Information Leaflet	n/a
Immediate container (blister)	n/a
Packaging tray	n/a

REVIEWER'S COMMENTS

Teva Women's Health, Inc., indicates it has accepted the majority of the Division's comments on the proposed cartons and consumer information leaflet exactly as communicated in the September 30, 2011 letter. The submitted labeling was compared to the draft labeling submitted February 7, 2011 and the currently approved labeling, dated July 10, 2009, that was approved as part of the original NDA submission.

A. Retail (Trade) Carton**i. Carton Label Outside Drug Facts**

The following changes have been made to the carton layout:

a. The location for the lot number and expiration date was moved from the bottom of the package next to the UPC code, to the left face of the package, due to limitations of the packaging machine.

This is acceptable.

b. The package has been rotated 180° so that it opens from right to left like a book.

This is acceptable.

c. On the interior portion of the carton, the three bullet points of text above the opening for the pill blister have been moved below this opening.

This is acceptable.

Listed below are FDA's September 30, 2011, labeling recommendations in bold, followed by the sponsor's response, and reviewer's comments in italics.

1. The statement (b) (4) is not acceptable. We consider this to be an inappropriate claim for an OTC product. Please remove this statement from the PDP.

Teva Women's Health, Inc. disagrees with the Division's comment and they note that (b) (4)

The claim has been maintained on both the PDP and the consumer information leaflet. (b) (4)

We believe that (b) (4) is an inappropriate claim for an OTC product. (b) (4)

We recommend that the claim (b) (4) be deleted.

2. We recommend that the strength be listed after the active ingredient name on the PDP to be consistent with other OTC drugs (i.e., "levonorgestrel 1.5 mg").

The sponsor has accepted this comment and the strength is now listed after the active ingredient as requested. This change is acceptable.

3. The phrase [REDACTED] (b) (4)

[REDACTED] (b) (4), *this is acceptable.*

4. The word [REDACTED] (b) (4) **is not acceptable in the labeling;** [REDACTED] (b) (4)

The Sponsor has replaced the word [REDACTED] (b) (4) *with the word “tablet” as requested. This is acceptable.*

5. The phrase [REDACTED] (b) (4) **is unclear and does not add anything to the approved labeling. We recommend that you use the originally approved language: “One Tablet One Dose” instead of** [REDACTED] (b) (4)

The Sponsor has modified the proposed language to read “One Tablet. One Step.”. This statement has been revised wherever it appears in the labeling. This is acceptable.

ii. Carton Drug Facts Label

[REDACTED] (b) (4)

8. A statement indicating that the product is “for women only” needs to be included on the carton or the Drug Facts section of the label. We recommend adding this information as the first bullet under the *Directions* section of Drug Facts.

The sponsor has elected to include the information “for women only” within the “Use” section of the **Drug Facts** as follows:

“Use for women to reduce chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)”.

This change is acceptable.

9. Under the **Other information** heading, [REDACTED] (b) (4)

The original language should be retained.

The original language was retained as requested. This is acceptable.

10. Remove the period from the end of bulleted statements comprised of only one statement (first and fifth bullets under **Other information**).

There are now 4 bullets under **Other information** since the STD alert bullet has been relocated to **Warnings**. The periods at the end of the bullets comprised of only one statement have been removed. This is acceptable.

iii. Immediate Container (Blister) Label

The sponsor has submitted the immediate container (blister card). The blister card is glued to the carton and is not visible to the consumer at the time of purchase. It contains the tablet identification and strength, lot number and expiration date. This is acceptable.

iv. Consumer Information Leaflet

The layout of the 4”x 6” leaflet has been altered from folding to a 3” x 4” booklet, to folding down into 2” x 2” size. This change was made so that the leaflet would better fit within the carton.

This is acceptable.

11. The statement [REDACTED] (b) (4) is not acceptable. We consider this to be an inappropriate claim for an OTC product. Please remove this statement from Consumer Information Leaflet as well.

We believe that [REDACTED] (b) (4)

We recommend that the claim [REDACTED] (b) (4) be deleted.

12. The word [REDACTED] (b) (4) is not acceptable. [REDACTED] (b) (4) See comment #4 above.

(b) (4) This is acceptable.

13. The claim (b) (4) is not acceptable. Replace the first sentence under the subheading “What Plan B One-Step is not” with the previously approved statement: “Plan B One-Step will not work if you are already pregnant and will not affect an existing pregnancy.”

The claim (b) (4) has been replaced by the previously approved statement “Plan B One-Step will not work if you are already pregnant and will not affect an existing pregnancy.” This is acceptable.

14. The proposed revision under the subheading “How does Plan B One-Step work?” is not acceptable. The original language should be used; however, changing “over 35 years” to “several decades” is acceptable. Change the word (b) (4) to “tablet” under this heading when referring to Plan B One-Step.

The proposed revision under “How does Plan B One-Step work” has been replaced with the original statement. “several decades” is used instead of “35 years” and the word (b) (4) is replaced by the word “tablet”. The changes are acceptable.

15. The proposed revision under the subheading “How can I get the best results from Plan B One-Step?” is not acceptable. With the exception of changing “a few days” to “72 hours (3 days)” for precision, this section should not be revised. The statement (b) (4)

Teva Women’s Health changed “a few days” to “72 hours (3 days)” and removed the word (b) (4) from the first sentence. They indicate that this provides an appropriate level of precision as to the time frame in which the product should be used. They have retained the phrase “after birth control failure or unprotected sex” instead of the currently approved “after unprotected sex”, as both situations represent appropriate usage of Plan B One-Step.

Although this revision is not as requested by FDA, these changes are acceptable. Stating that “You have 72 hours (3 days) to try to prevent pregnancy...” is consistent with the rest of the labeling for this product.

16. Under the subheading “How will I know (b) (4) Plan B One-Step worked?, remove the word (b) (4) from the subheading and revise the first sentence to read as follows: “You will know Plan B One-Step worked when you get your next period, which should come at the expected time, or within a week of the expected time.”

The word (b) (4) has been removed from the subheading. This is acceptable. The first sentence was not revised as requested. The first sentence now reads: “You will know Plan B One-Step has been effective when you get your next period, ...”. The phrase “has been effective” is used instead of “worked” in the first sentence. We had recommended the word

“worked” for consistency with the subheading. The phrase “has been effective” has the same meaning as “worked” and is acceptable.

17. Under the subheading “Will I experience any side effects?”, we recommend bulleted statements to improve clarity and to highlight important information. Move the statement about a missed period to be the first statement since it is important information. Modify this section to read as follows:

“● some women may have changes in their period, such as a period that is heavier or lighter or a period that is early or late. If your period is more than a week late, you may be pregnant.

● if you have severe abdominal pain, you may have an ectopic pregnancy, and should get immediate medical attention.

● when used as directed, Plan B One-Step is safe and effective. Side effects include changes in your period, nausea, lower stomach (abdominal) pain, tiredness, headache, dizziness, and breast tenderness.

● if you vomit within 2 hours of taking the medication, call a healthcare professional to find out if you should repeat the dose.”

The Sponsor has revised the information under this subheading as requested, with one minor revision. Under the third bullet, the second sentence reads: “Side effects may include...” rather than “Side effects include...”. This is acceptable.

B. Packaging Tray

The sponsor submitted a new piece of secondary packaging called a packaging tray. The packaging tray will hold six (6) retail cartons for shipping to retail customers. After removal of the top and most of the front of the package, the full tray is intended to be placed directly on the shelf for access by customers. As the lower portion of the front of the tray will cover the lower portion of the Principal Display Panel of the retail carton, if full, the packaging tray labeling reflects the text that would be obscured.

The front panel of the secondary packaging tray is consistent with the design of the PDP on the retail carton except for the statement on the lower left side of the PDP indicating it “Contains 1 Tablet 1.5 mg” and on the top left side of the PDP indicating (b) (4)

Overall, the packaging tray is acceptable; however, we believe that (b) (4) is an inappropriate claim for an OTC product. We recommend that the claim (b) (4) be deleted from the front panel of the packaging tray.

The phrases “Plan B One-Step”, “levonorgestrel 1.5 mg”, “emergency contraceptive”, and “One Tablet. One Step.” are repeated on the side panels and top panel.

This is acceptable.

III. RECOMMENDATIONS

Due to the above-mentioned labeling deficiencies, we cannot recommend approval at this time. We currently recommend a Complete Response action pending the resolution of the following labeling deficiencies:

1. We believe that [REDACTED] ^{(b)(4)} is an inappropriate claim for an OTC product. We recommend that the claim [REDACTED] ^{(b)(4)} be deleted from the labeling wherever it appears.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

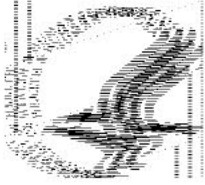
5 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARIA E YSERN
10/27/2011

COLLEEN K ROGERS
10/27/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Office of New Drugs – Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

Date: October 4, 2011

From: Lisa Mathis, M.D., OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Lesley-Anne Furlong, M.D., M.S., Clinical Team Leader, DNCE

Re: Levonorgestrel tablet 1.5 mg/Plan B One-Step

NDA: 21-998 S002

Applicant: Teva Women’s Health, Inc.

Indication: Plan B One-Step is a progestin-only emergency contraceptive indicated for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure.

Proposed Dose: One tablet taken orally as soon as possible within 72 hours after unprotected intercourse

Consult Request

“The applicant seeks to change the marketing status of Plan B One-Step from prescription (Rx) to over-the-counter (OTC) for women who are younger than 17 years old. Plan B One-Step is currently approved OTC for women who are at least 17 years of age and by prescription for those ages 16 years and younger.

To support nonprescription availability for those less than 17 years old, FDA directed the applicant to address Dr. Galson’s issues as enumerated in his memos regarding the

related product, Plan B, dated 6-May-2004 and 26-Aug-2005 (see attached). Dr. Galson involved the pediatric staff in preparing his opinions. A series of reviews, meetings, and agreements (in which DNCE, Dr. Galson, others from upper management, and pediatrics participated) resulted in the advice FDA provided to Teva and, thus, in the present submission.

Consequently, to support the expansion of the OTC population, the applicant has provided a label comprehension study, an actual use study, a literature review, and a postmarketing safety update. The applicant does not propose any changes in the product, its indication, its dosing regimen, or the population for whom it is indicated. If this supplemental NDA is approved, women less than 17 will be able to access the product OTC. The DNCE's review is ongoing.

Please look at the provided documents and provide comments if you deem necessary.”

A. Regulatory Background

Plan B was originally approved as a prescription product in 1999. An application for Plan B One-Step (levonorgestrel) tablet 1.5 mg was submitted on January 24, 2006 (NDA 21-998). The product was approved on July 10, 2009 with dual marketing status based on the approval of Plan B (NDA 21-045, the same product with a 2 tablet dosing regimen). Currently, both Plan B and Plan B One-Step are marketed OTC for patients age 17 and older, and by prescription (Rx) for patients age 16 and under. This supplement seeks to make Plan B One-Step available Over the Counter (OTC) for all women of child-bearing potential.

The original Plan B application (NDA 21-045) was first approved as a prescription product in 1999. Subsequently, Plan B was approved with dual marketing status (OTC for 18 and older, prescription for under 18) based on the concern by Dr. Steven Galson, CDER Center Director at the time, that the application did not have enough pediatric patients ages 11-17 years to assess the safe OTC use of the product in this population. In 2009, both Plan B and Plan B One-Step were labeled as prescription products for teens younger than 17 years of age. A letter was written dated 8/26/2005 outlining the deficiencies that needed to be addressed prior to consideration of OTC status for younger pediatric patients. The Sponsor has responded to all of the informational needs as outlined in the memo by Dr. Galson.

The studies submitted by the Sponsor were agreed upon with the FDA after multiple meetings and other interactions as studies that would address the deficiencies outlined in Dr. Galson's memo of 8/26/2005.

B. Brief Synopsis of Applicant's Clinical Program

This product is already approved as a prescription product, and thus the safety and efficacy in the pediatric population have been established. Additional data were needed

to support that the benefits and risks would be the same if the product was available OTC without a learned intermediary. The studies required for an Rx to OTC switch for the pediatric population, as agreed upon prior to submission of this application, consisted of a Label Comprehension Study and an Actual Use Study.

The Label Comprehension Study was designed to assess whether younger women could understand six key elements of OTC labeling. The Actual Use Study was designed to evaluate the patient's ability to self-diagnose the condition and assess that the treatment with the product was appropriate for them, and the patient's ability to self-treat with the product according to the product instructions. The study also assessed the patient's ability to self-manage following treatment.

Label Comprehension Study DR-LEV-301

The label comprehension study was designed to determine whether, by reading the package label, young women aged 12-17 years can understand the information needed for safe and effective use of Plan B One-Step. The specific key communication objectives assessed were:

1. Plan B One-Step is indicated for prevention of pregnancy after unprotected sex.
2. Plan B One-Step should be taken as soon as possible after sex.
3. Plan B One-Step does not prevent sexually transmitted diseases or HIV/AIDS
4. Plan B One-Step should not be used in place of regular contraception.
5. Plan B One-Step should be taken within 72 hours after sex.
6. Plan B One-Step should not be used by women who are already pregnant.

Subjects were recruited at shopping malls and clinics in 8 large metropolitan areas in the U.S., by trained female interviewers. After consent was obtained from the subject's parent, subjects were given a prototype OTC package to read. The interviewer then administered a questionnaire to test understanding of the key concepts; these questions included both straightforward questions about information on the package and descriptions of scenarios in which the subject had to determine whether the product was or was not used correctly according to the information on the package. Demographic information was collected following the questionnaire, including race, educational level, and sexual and contraceptive experience.

The study planned to enroll a minimum of 50 subjects of each age 12-17 years, inclusive. In addition, to ensure demographic diversity, a minimum of 75 subjects (25% of the planned sample) were to be African American and a minimum of 60 subjects (20% of the planned sample) were to be Hispanic. A minimum of 60 subjects who tested at 7th grade literacy or lower was to be enrolled, to ensure sufficient oversampling of subjects with lower literacy. Finally, to minimize influence of prior provider counseling on EC, at least 225 subjects (75% of the planned sample) should not have used EC before.

Number of patients: The study consisted of 335 female subjects between the ages of 12-17 years inclusive. Each age group included between 54 and 59 subjects with age group

15 having the largest number of subjects (59) and age groups 12 and 14 having the smallest number of subjects (54).

The study results were reviewed by Murewa Oguntimein, MHS, CHES, who concluded that this was a “thorough, well-designed label comprehension study with the adequate sample size between age 12-17 inclusive. The study achieved pre-specified objectives by estimating the proportion of young women aged 12-17 years, inclusive, who demonstrate an understanding of six key concepts of OTC labeling. Most subjects comprehended the six key concepts (82.7%-95.5%), with key concept 2 (Plan B® 1.5 should be taken as soon as possible after sex) being the least understood.”

“The study demonstrated that adolescents were able to understand the key elements of the label. The approval of this NDA supplement will also depend on how well the label translates to safe and appropriate use of the product in the actual use study, which will be determined by the evaluation of the actual use study.”

“The labeling elements tested are acceptable based on the results of this study. In the proposed label, the sponsor has added prominent text to emphasize the importance of taking the product as soon as possible; this is acceptable.”

Actual Use Study (DR-LEV-302)

DR-LEV-302 was a non-comparative, open-label, single use, multicenter case series to assess the ability of patients 11-17 years of age to appropriately self-select and correctly use Plan B One-Step. This study design was discussed with the FDA, and it was agreed that the protocols were sufficient to answer outstanding questions about the use of this product in adolescent patients.

This actual use study was designed to evaluate whether young women age 11-17 could appropriately self-select whether to use Plan B One-Step, and use it correctly, in a simulated OTC setting. Subjects were to make their decisions based only on the information on the label, and without provider counseling.

Patients 11 – 17 years of age who presented at one of the participating clinics and spontaneously requested EC were made aware of the study and offered further screening, via a standardized script. A brief Screening Questionnaire assessed whether the potential subject met the inclusion criteria (age, in need of EC for herself, ability to understand English, and willingness to participate in the study). Patients who continued to qualify for the study signed an informed consent form and were considered “Enrolled.” They were then asked to fill out the first part of the Participant Questionnaire and provide the reason why they were seeking EC.

Enrolled subjects were presented a package of “Plan B 1.5” and asked to read it. They were then asked to complete the remainder of the Participant Questionnaire and indicate whether they wanted to use the product, and if not, why not. Finally, they completed a

Baseline Questionnaire to collect demographic information and selected obstetric and gynecologic history.

At this point study staff reviewed all of the questionnaires, and determined whether the subject had appropriately or inappropriately self-selected. Subjects who were determined to have inappropriately selected to use the product, or to have appropriately selected not to use the product, were referred back to the clinic and were not followed up further.

Subjects who were determined to have appropriately self-selected to use the product were given one package of study medication. Subjects were contacted by study staff approximately one week later and asked whether they had used the product. If they had, they were then asked when they took it, and when their unprotected intercourse had occurred. If they had not taken the product, they were asked why not. At this point, correct or incorrect use of the product was determined. If subjects were not able to be contacted at one week but were contacted subsequently, information about use was collected for the purpose of determining drug exposure only. Recall of the time the drug was taken and the time of the unprotected intercourse was considered to be unreliable given the greater elapsed time. Safety was assessed during each follow-up contact by questioning subjects about any health problems since their last contact. If a subject reported a pregnancy, she was followed up until pregnancy outcome.

A total of 343 patients were enrolled (11- 13 year, 3 patients; 14 years, 35 patients; 15 years, 100 patients; 16 years, 140 patients; 17 years, 65 patients). According to the applicant's analysis, a total of 307 of 343 enrolled subjects (89.5%) appropriately self-selected to use Plan B One-Step. Of these, 263 (85.7%) reported at the One Week Follow-Up Visit that they had used it correctly according to the package label.

Although there was a low number of patients from ages 11-13 years, the percentage of the total is consistent with the use of these products in this age group. The condition and the response to therapy in patients in this age group is expected to be sufficiently similar to patients in the 14 year old age group, and thus the data from that age group can be used to support the ability of younger patients to use the medication appropriately.

The FDA clinical review team has independently analyzed the data and found that own 341 out of 343 appropriately self-selected (99.99%) and out of the 297 subjects who actually took the drug, 274 took it correctly (92.3%). The performance of the adolescents also compared favorably with the adult AUS that supported the Plan B application.

No new safety signals were identified in the studies. All adverse events were consistent with current labeling. The most frequently reported AEs were headache, nausea, and menstrual irregularity.

C. PMHS Discussion and Recommendations

PMHS recommends the approval of this application to expand OTC marketing to all females of child bearing potential based on the data submitted in this application.

As stated previously, this product was previously determined to be safe and effective in the pediatric population as a prescription product. The outstanding question was whether Plan B One Step is safe and effective when used in an OTC setting by adolescent patients.

The deficiencies that needed to be addressed were outlined in the memos by Dr. Galson dated May 6, 2004 and August 26, 2005. With this submission, the Sponsor has fully responded to the data needs as outlined in these memos. In the May 6, 2004 memo, it was noted that there were no patients less than age 14 years and that, based on developmental differences, it would not be possible to extrapolate data from the population 14 years and older to the population 11 – 14 years of age. The studies submitted included patients in age subgroups proportionate to the population likely to use this product if approved. DR-LEV-301 enrolled 110 patients under 14 and DR-LEV-302 enrolled 3 patients under 14.

The studies provide data to demonstrate that woman of child bearing potential of all ages can appropriately self-diagnose and administer Plan B One-Step in an OTC setting. No new safety concerns that were identified. This information has been reviewed in the context of other available data on the OTC use of Plan B products OTC. The safety and efficacy of OTC Plan B One-Step in this subpopulation is supported by the totality of the data submitted to support the application.

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/s/

LISA L MATHIS
10/11/2011

Labeling Review for Plan B One-Step (levonorgestrel) tablet, 1.5 mg *Draft Labeling*

SUBMISSION DATES: February 7 and March 31, 2011

NDA/SUBMISSION TYPE: NDA 21-998. Efficacy Supplement S-002

ACTIVE INGREDIENT: Levonorgestrel, 1.5 mg

DOSAGE FORM: Tablet

SPONSOR: TEVA/ Teva Women's Health
415 Privet Road, P.O. Box1005, PA 19044-8005
Phone: 215-293-6200
Contact: Valerie M. Mulligan, Senior Director, Regulatory Affairs

REVIEWER: Maria Ysern, IDS, DNRD, ODE IV

TEAM LEADER: Colleen Rogers, PhD, DNRD, ODE IV

PROJECT MANAGER Melissa H. Furness, Chief Project Manager, DNCE, ODE IV

I. BACKGROUND

NDA 21-998 for Plan B One-Step (Levonorgestrel Tablet 1.5 mg) was approved July 10, 2009. March 23, 2009, a federal court issued an order to FDA directing the Agency to allow (then) Duramed to make Plan B (a two tablet, levonorgestrel-containing product with a different strength and dosing regimen, marketed by the sponsor) available OTC for 17 year olds, and to reconsider its denial of the 2001 Citizen's Petition that asked for full OTC access for Plan B. On April 21, 2009, the Agency issued the Sponsor an Advice Letter indicating that the Agency had concluded that the scientific evidence supported allowing the Plan B product being made available OTC for those 17 years and older, and requesting that the Sponsor submit an efficacy supplement with a revised label to reflect the new age split. In addition, the Agency requested that the Sponsor reflect the same age split in the pending application for the single tablet Plan B One-Step product.

On July 10, 2009 FDA approved Plan B One-Step NDA 21-998 with prescription (Rx) availability of Plan B One-Step for women younger than 17 years, and with OTC availability of Plan B One-Step for women age 17 and older.

The purpose of this efficacy supplement is to request a change in population for whom the single tablet Plan B One-Step product is available as an over the counter (OTC) product. This efficacy supplement consists of a report of a new clinical investigation: a single clinical study on adolescent females, age 11-17 years. This multicenter, non-comparative study was conducted to evaluate the ability of these females, who are voluntarily requesting emergency contraception, to use the single tablet Plan B One-Step product in a safe and appropriate manner without provider counseling. The sponsor states that the clinical study was specifically designed to evaluate the appropriateness of an Rx-to-OTC switch for the single tablet Plan B-One Step product only.

Submitted Labeling	Representative of Following SKUs
Carton label, Clinic	n/a
Carton label, Trade	n/a
Consumer Information Leaflet	n/a

The proposed labeling was compared to the currently approved labeling (dated July 10, 2009) that was approved as part of the original NDA 21-998 submission.

II. REVIEWER'S COMMENTS

A. Retail Carton (Trade Box Wallet Carton)

i. Outer Carton Label Outside Drug Facts

- a. The “wallet” carton has been changed from a horizontal (landscape) orientation to a vertical (portrait) orientation. The carton retains a 2-panel fold-out inner panel that contains the blister-sealed tablet.

This change in format is acceptable.

- b. The color scheme of the carton has been changed from green to blue; however, the color scheme retains pink accents.

This change is acceptable.

- c. The top left corner of the principal display panel (PDP) and the top right corner of the carton back panel contain the following statement: (b) (4)

This is acceptable; however, the statement will need to be removed after six months of marketing.

- d. The NDC number has been moved from the top left corner of the PDP to the top right corner of the PDP. The NDC number has changed.

This is acceptable.

- e. The statement “Rx only for women younger than age 17” was removed from the PDP and side panels.

This change is acceptable since, if approved, it will be an OTC product for women of all ages. However, a statement indicating that the product is “for women only” needs to be included on the carton or the Drug Facts section of the label.

- f. On the left top side of the PDP, the following statement has been added:

(b) (4)

(b) (4) *is not acceptable. Please remove this statement. We consider this to be an inappropriate claim for an OTC product due to its promotional nature.*

- g. The active ingredient, dosage form, and strength was changed from: “(levonorgestrel) tablet, 1.5 mg” to “(b) (4)” on the PDP.

This change is not acceptable. (b) (4)

- h. On the PDP, following the phrase (b) (4)

This is not acceptable. (b) (4)

- i. On the right lower side of the PDP, the phrase “One Tablet One Dose” has been changed to:

(b) (4)

The word “(b) (4)” is not acceptable. (b) (4)

We recommend that the sponsor use the originally approved language “One Tablet One Dose”.

- j. The phrase “(b) (4)” has been added to the carton side panels, back panel, and inner panels.

This is not acceptable. See comments at II.A.i.i.

- k. The phrase [REDACTED] (b) (4) [REDACTED] has been moved from the right side of the PDP to the back panel of the carton (next to Drug Facts) and reworded as follows:
“The sooner you take it, the more effective it will be
Take as soon as possible within 72 hours (3 days) after unprotected sex
Will not harm an existing pregnancy”

These revisions are acceptable.

- l. The phrase “Visit us at: www.PlanBOneStep.com” has been added to the bottom left corner of the back panel of the carton.

This is acceptable.

- m. The manufacturer information has been moved from the back panel to the bottom panel of the carton and updated to reflect the current sponsor.

This is acceptable.

- m. The phrase “• [REDACTED] (b) (4) [REDACTED] on the inner panel has been revised to 3 bulleted statements, which are reworded as described in II.A.i.k.

These revisions are acceptable.

- n. The phrases [REDACTED] (b) (4) [REDACTED]

This is acceptable since this information is found elsewhere in the labeling.

ii. Outer Carton Drug Facts Label

a. Warnings

- 1. [REDACTED] (b) (4) [REDACTED]

This change is not acceptable. [REDACTED] (b) (4) [REDACTED]

2. Do not use

The second bullet, [redacted] (b) (4)

This is not acceptable. [redacted] (b) (4)

b. Directions

This section was modified by removing the Rx information for women younger than 17 (first and last bullets). The directions are now the same for women of all ages, and read as follows:

- “• take as soon as possible within 72 hours (3 days) after unprotected sex. The sooner you take it the better it will work.
- if you vomit within 2 hours after taking the medication, call a healthcare professional to find out if you should repeat the dose”

This change is acceptable since Plan B One-Step will no longer be available by prescription if this supplement is approved. We also recommend that a first bullet be added which would state that the product is “for women only” (see II.A.i.e).

c. Other information

1. The first bullet has been changed from:

“• **before using this product read the enclosed consumer information leaflet for complete directions and information**”

to:

“• **read the instructions, warnings and enclosed product leaflet before use.**”

This change is acceptable; however, the period should be removed since there is only a single statement after the bullet.

2. The second bullet has been changed from:

“• this product is not recommended for regular birth control. It does not work as well as most other birth control methods used correctly.”

to:

“• [redacted] (b) (4)

This change is acceptable.

3. The third bullet was [redacted] (b) (4)

[redacted] (b) (4)

(b) (4)
The
original language should be retained.

4. The fourth bullet was deleted:

“• when used correctly every time you have sex, latex condoms greatly reduce, but do not eliminate, the risk of pregnancy and the risk of catching or spreading HIV, the virus that causes AIDS. See condom labeling for additional STD information.”

This change is acceptable.

5. (b) (4)

This is not acceptable. See II.A.ii.a.1.

6. The fifth bullet has been changed from: “• tablet is enclosed in a blister seal. **Do not use if the blister seal is broken.**” to: “• **do not use if carton is open or tear strip is removed or blister seal is broken or missing.**”

This change is acceptable; however, the period should be removed since there is only a single statement after the bullet.

iii. Immediate Container Label

The immediate container consists of a PVC and aluminum blister, which is attached to the inner panel of the carton.

The sponsor did not provide the immediate container label. Request that the sponsor submit the immediate container (blister card) label for review.

iv. Consumer Information Leaflet

In this supplement, the sponsor proposes to make Plan B One-Step nonprescription for women of all ages. Consequently, if approved, the package insert will be discontinued and has not been submitted. The previously approved CIL was formatted as a 25-page booklet. The currently proposed CIL is formatted as a single page folded into a 4-page booklet.

To facilitate the review of the changes to the CIL, the sponsor provided a table with the text from the current CIL, the proposed CIL, and the rationale for the changes. For ease of review, we will use this table to indicate changes.

a. The cover page of the CIL, on the top left side, has the statement: “#1 Doctor recommended”.

(b) (4) is not acceptable. Please remove this statement. We consider this to be an inappropriate claim for an OTC product.

b.

CURRENT CIL	PROPOSED CIL	RATIONALE
<p>Plan B® One-Step Emergency Contraceptive. Because the unexpected happens. Important information about Plan B® One-Step, Birth Control & Sexually Transmitted Diseases For additional information intended for healthcare professionals, please see enclosed Product Information for Plan B® One-Step.</p>		(b) (4)

(b) (4)

c.

<p>Plan B® One-Step logo From the makers of Plan B®, Duramed Pharmaceuticals, Inc., a subsidiary of Barr Pharmaceuticals, Inc.</p>	<p>Plan B One-Step® logo Teva Women's Health, Inc.</p>	<p>Logo updated. Company name changed.</p>
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This update of the manufacturer's information is acceptable.

d.

<p>What is Plan B® One-Step? Plan B® One-Step is emergency contraception that helps prevent pregnancy after birth control failure or unprotected sex. It is a backup method of preventing pregnancy and is not to be used routinely. Plan B® One-Step can reduce your chance of</p>	<p>What is Plan B One-Step®? Plan B One-Step® is emergency contraception that helps prevent pregnancy after birth control failure or unprotected sex. It is a backup method of preventing pregnancy and should not be used as regular birth control.</p>	<p>"is not to be used routinely" changed to "should not be used as regular birth control" for clarity. Second paragraph removed from this section as it does not directly apply. Relocated information to section "When should I use Plan B One-</p>
<p>pregnancy after unprotected sex (if your regular birth control was used incorrectly or fails, or if you have had sex without birth control). For example, if you were using a condom and it broke or slipped, if you did not use your regular birth control as you should have, or if you did not use any birth control, Plan B® One-Step may work for you.</p>		<p>Step®?</p>

These changes are acceptable.

e.

<p>What Plan B® One-Step is not.</p> <p>Plan B® One-Step will not work if you are already pregnant and will not affect an existing pregnancy.</p> <p>Plan B® One-Step should not be used as regular birth control. It is important to have another reliable source of birth control that is right for you. Plan B One-Step will not protect you from HIV infection (the virus that causes AIDS) and other sexually transmitted diseases.</p>	<p>(b) (4)</p>
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(b) (4)

replace the first sentence with the previously approved statement: “Plan B One-Step will not work if you are already pregnant and will not affect an existing pregnancy.” The second sentence is acceptable.

f.

<p>When is the appropriate time to use Plan B® One-Step?</p> <p>You can use Plan B® One-Step <u>after</u> you have had unprotected sex in the last 72 hours (3 days), and you do not want to become pregnant.</p> <p>Plan B® One-Step can be used as a backup or emergency method to regular birth control if, for example,</p> <ul style="list-style-type: none"> Your regular birth control method was used incorrectly or failed (your partner’s condom broke or slipped) You made a mistake with your regular method You did not use any birth control method 	<p>When should I use Plan B One-Step®?</p> <p>The sooner you take emergency contraception, the better it works. You should use Plan B One-Step® within 72 hours (3 days) <u>after you have had unprotected sex</u>.</p> <p>Plan B One-Step® is a backup or emergency method of birth control you can use when:</p> <ul style="list-style-type: none"> your regular birth control was used incorrectly or failed you did not use any birth control method 	<p>Changed heading for clarity</p> <p>Added statement “the sooner you take emergency contraception, the better it works” to highlight the importance of taking it as soon as possible.</p> <p>Added visual stress to statement “after you have had unprotected sex” for clarity that it is not to be used prior to intercourse.</p> <p>Simplified bulleted list to reduce confusion</p>
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The change of the heading makes it clearer. The proposed first sentence helps clarify that it should be used sooner rather than later. Underlining the statement after you have had unprotected sex helps clarify that it is not used before intercourse. The changes are acceptable.

g.

<p>When is it not appropriate to use Plan B One-Step®</p> <ul style="list-style-type: none"> Plan B One-Step should not be used as a regular birth control method. It does not work as well as most other forms of birth control when they are used consistently and correctly. Plan B One-Step is a <u>backup or emergency</u> method of contraception. Plan B One-Step should not be used if you are already pregnant because it will not work. Plan B One-Step should not be used if you are allergic to levonorgestrel or any other ingredients in Plan B One-Step. Plan B One-Step does not protect against HIV (the virus that causes AIDS) or other sexually transmitted diseases (STDs). The best ways to protect yourself against getting HIV or other STDs is to use a latex condom correctly with every sexual act or not to have sex at all. 	<p>When not to use Plan B One-Step®.</p> <p>Plan B One-Step® should not be used:</p> <ul style="list-style-type: none"> as a regular birth control method, because it's not as effective as regular birth control. if you are already pregnant, because it will not work. if you are allergic to levonorgestrel or any other ingredients in Plan B One-Step®. 	<p>Changed heading for clarity.</p> <p>Moved "Plan B One-Step® should not be used" outside of bulleted statements for clarity.</p> <p>Removed statement that Plan B One-Step is a backup/emergency method because that does not apply to heading of when <u>not</u> to use.</p> <p>Removed bullet regarding STDs because information already in section "What Plan B One-Step® is not"</p>
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The proposed revisions provide clarity. These changes are acceptable.

h.

<p>How does Plan B One-Step® work?</p> <p>Plan B One-Step is one pill with levonorgestrel, a hormone that has been used in many birth control pills for over 35 years. Plan B One-Step contains a higher dose of levonorgestrel than birth control pills, but works in a similar way to prevent pregnancy. It works mainly by stopping the release of an egg from the ovary. It is possible that Plan B One-Step may also work by preventing fertilization of an egg (the uniting of sperm with the egg) or by</p>	<p>How does Plan B One-Step® work?</p> <p>Plan B One-Step® is one pill with levonorgestrel, a hormone that has been used in many birth control pills for several decades. Plan B One-Step contains a higher dose of levonorgestrel than birth control pills, but works in a similar way to prevent pregnancy. It works mainly by stopping the release of an egg from the ovary.</p>	<p>"over 35 years" changed to "several decades" for simplification.</p> <p>Mechanism of action statement reduced to only refer to primary mechanism and not refer to speculative mechanisms.</p>
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The proposed revision is an over-simplification and is not acceptable. Replace with the previously approved paragraph, except replace the word "(b) (4)" with "tablet" (see II.A.i.i). Changing "over 35 years" to "several decades" is acceptable.

i.

<p>How can I get the best results from Plan B One-Step®</p> <p>You have only a few days to try to prevent pregnancy after unprotected sex. The sooner you take Plan B One-Step, the better it works. Plan B One-Step should be taken as soon as possible within 72 hours (3 days) after unprotected sex.</p>	<p>(b) (4)</p>
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The proposed revision is not acceptable. (b) (4)



(b) (4) *With exception to changing “a few days” to “72 hours (3 days)”, this section should not be revised.*

j.

<p>How effective is Plan B® One-Step?</p> <p>The sooner you take Plan B® One-Step, the better it will work. Take Plan B® One-Step as soon as possible after unprotected sex. If it is taken as soon as possible within 72 hours (3 days) after unprotected sex, it will significantly decrease the chance that you will get pregnant. Seven out of every 8 women who would have gotten pregnant will not become pregnant.</p>	<p>How effective is Plan B One-Step®?</p> <p>If Plan B One-Step® is taken as directed, it can significantly decrease the chance that you will get pregnant. About 7 out of every 8 women who would have gotten pregnant will not become pregnant.</p>	<p>First two sentences removed because they were redundant to previous section.</p> <p>“taken as soon as possible within 72 hours (3 days) after unprotected sex” changed to “taken as directed” for simplification.</p>
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The proposed revision is acceptable.

k.

<p>How will I know if Plan B® One-Step worked?</p> <p>Most women will have their next menstrual period at the expected time or within a week of the expected time. If your menstrual period is delayed beyond 1 week, you may be pregnant. You should get a pregnancy test and follow up with your healthcare professional.</p>	<p>(b) (4)</p>
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1. *Revise the section title to remove the word “(b) (4)”*
2. *Revise the first sentence to read as follows: “You will know Plan B One-Step worked when you get your next period, which should come at the expected time, or within a week of the expected time.”*

l.

<p>What if I am already pregnant and use Plan B® One-Step?</p> <p>There is no medical evidence that Plan B® One-Step would harm a developing baby. If you take Plan B® One-Step (accidentally) after you are already pregnant or it does not work and you become pregnant, it is not likely to cause any harm to you or your pregnancy. The pregnancy will continue. Plan B® One-Step will not work if you are already pregnant.</p>	<p>This section has been removed in the Proposed CIL</p>	<p>Information that Plan B One-Step will not affect an existing pregnancy is already present in “What Plan B One-Step® is not” section.</p>
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We agree with the rationale provided. The proposed revision is acceptable.

m.

<p>What should I do if my menstrual period is delay beyond 1 week and I have severe lower stomach (abdominal) pain?</p> <p>If you have severe lower stomach (abdominal) pain about 3 to 5 weeks after taking Plan B® One-Step, you may have a pregnancy outside the uterus, which is called a tubal pregnancy. A tubal pregnancy requires immediate medical treatment, so you should see a healthcare professional right away.</p>	<p>This section has been removed in the Proposed CIL</p>	<p>Ectopic pregnancy warning moved to “Will I experience any side effects?” section.</p>
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This information was moved to the section “Will I experience any side effects?”. The proposed revision is acceptable.

n.

<p>Can I use Plan B® One-Step for regular birth control?</p> <p>No. Plan B® One-Step should <u>not</u> be used for regular birth control. It is an emergency or backup method to be used if your regular birth control fails or is used incorrectly or if you have sex without birth control. You should protect yourself against STDs and pregnancy every time you have sex. If you have unprotected sex again after taking Plan B® One-Step, it will not help protect you from getting pregnant.</p>	<p>This section has been removed in the Proposed CIL</p>	<p>Deleted due to redundancy. Deleted advice about regular birth control and preventing STDs as it is not applicable to correctly using Plan B One-Step®.</p>
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The proposed deletion is acceptable.

o.

<p>How often can I use Plan B® One-Step?</p> <p>Plan B® One-Step is meant for emergency protection only, and is not designed to be used frequently. If you find that you need to use emergency contraception often, talk to your healthcare professional and learn about methods of birth control and STD prevention that are right for you.</p>	<p>This section has been removed in the Proposed CIL</p>	<p>Deleted due to redundancy. Deleted advice about regular birth control and preventing STDs as it is not applicable to correctly using Plan B One-Step®.</p>
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The proposed deletion is acceptable.

p.

Will I experience any side effects from Plan B® One-Step?

When used as directed, Plan B® One-Step is safe for women. Some women will have mild, temporary side effects, such as menstrual changes, nausea, lower stomach (abdominal) pain, tiredness, headache, dizziness, breast pain and vomiting. These are similar to the side effects that some women have when taking regular birth control pills. Some women taking Plan B® One-Step will have menstrual changes such as spotting or bleeding before their next period. Some women may have a heavier or lighter next period, or a period that is early or late. **If your period is more than a week late, you should get a pregnancy test.**



As proposed, some important information is not easily visible. We recommend bulleted statements to improve clarity and to highlight important information. We also recommend moving the statement about a missed period to be the first statement since this is important information.

Modify this section to read as follows:

- “• some women may have changes in their period, such as a period that is heavier or lighter or a period that is early or late. **If your period is more than a week late, you may be pregnant.***
- if you have severe abdominal pain, you may have an ectopic pregnancy, and should get immediate medical attention*
- when used as directed, Plan B One-Step is safe and effective. Side effects include changes in your period, nausea, lower stomach (abdominal) pain, tiredness, headache, dizziness, and breast tenderness.*
- if you vomit within 2 hours of taking the medication, call a healthcare professional to find out if you should repeat the dose”*

q.

<p>What warnings should I know about when using Plan B® One-Step? Plan B® One-Step does not protect against the AIDS virus (HIV) or other sexually transmitted diseases (STDs).</p>	<p>This section has been removed in the Proposed CIL</p>	<p>Removed for redundancy.</p>
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The proposed deletion is acceptable.

r.

<p>Do not use:</p> <ul style="list-style-type: none"> • If you are already pregnant (because it will not work) 	<p>This section has been removed in the Proposed CIL</p>	<p>Removed for redundancy.</p>
<ul style="list-style-type: none"> • If you are allergic to levonogestrel or any of the ingredients in Plan B® One-Step • For regular birth control 		

The proposed deletion is acceptable.

S.

<p>When using this product, you may have:</p> <ul style="list-style-type: none"> • Menstrual changes • Nausea • Lower stomach (abdominal) pain • Tiredness • Headache • Dizziness • Breast pain • Vomiting 	<p>This section has been removed in the Proposed CIL</p>	<p>Removed for redundancy.</p>
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The proposed deletion is acceptable.

t.

<p>Keep out of reach of children: In case of overdose, get medical help or contact a Poison Control Center right away at 1-800-222-1222.</p>	<p>This section has been removed in the Proposed CIL</p>	<p>Information relocated to “Other Information” section.</p>
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The relocation of this statement is acceptable.

u.

<p>What are the directions for using Plan B® One-Step? Women 17 years of age and older:</p> <ul style="list-style-type: none"> • Take Plan B® One-Step as soon as possible within 72 hours (3 days) after unprotected sex. • If you vomit within 2 hours of taking the medication, call a healthcare professional to find out if you should repeat the dose. <p>Prescription only for women younger than age 17. If you are younger than age 17, see a healthcare professional.</p>	<p>This section has been removed in the Proposed CIL</p>	<p>Removed for redundancy.</p>
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The proposed deletion is acceptable.

v.

<p>What should I do if I have questions about Plan B® One-Step? If you have questions or need more information about this product, call our toll-free number, 1-800-330-1271, visit our website at www.PlanBOneStep.com, or ask a healthcare professional.</p>	<p>What if I still have questions about Plan B One-Step®? If you have questions or need more information, call our toll-free number, 1-800-330-1271, or visit our website at www.PlanBOneStep.com.</p>	<p>Removed direction to ask a healthcare professional as this is no longer a prescription product.</p>
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The proposed change is acceptable for the reasons proposed.

W.

<p>Other information Tablet is enclosed in a blister seal. Do not use if the blister seal is broken. Store at room temperature 20–25°C (68–77°F). You may report side effects to FDA at 1-800-FDA-1088.</p>	<p>Other Information Keep out of reach of children: In case of overdose, get medical help or contact a Poison Control Center right away at 1-800-222-1222. Do not use if the blister seal is opened. Store at room temperature 20–25°C (68–77°F).</p>	<p>“Keep out of reach of children” moved to this section</p>
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The proposed revision is acceptable.

X.

<p>Active ingredient: levonorgestrel 1.5 mg Inactive ingredients: colloidal silicon dioxide, potato starch, magnesium stearate, talc, corn starch, lactose monohydrate</p>	<p>Active ingredient: levonorgestrel 1.5 mg Inactive ingredients: colloidal silicon dioxide, potato starch, magnesium stearate, talc, corn starch, lactose monohydrate</p>	<p>No change</p>
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There have been no changes to this section and this is acceptable.

Y.

<p>Protect yourself in more ways than one! If you are sexually active, but you are not ready for a pregnancy, it is important to use regular pregnancy protection. There are many types of birth control. Whichever type you choose, it is important to use your regular birth control method as directed. This ensures that you have effective protection against pregnancy every time you have sex. But things do not always go as planned. For</p>	<p>This section has been removed in the Proposed CIL</p>	<p>Removed for redundancy. Reference to using other regular birth control and avoiding STDs is not applicable to the correct use of the product.</p>
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example, if you were using a condom and it broke or slipped, or if you did not use your regular birth control as you should have, or if you did not use any birth control, Plan B® One-Step may work for you. Plan B® One-Step is an emergency contraceptive that helps prevent pregnancy after unprotected sex or when your birth control fails or is not used correctly.

Remember, Plan B® One-Step is only for emergency pregnancy prevention. There are many other products that work for regular birth control that are available by prescription or over-the-counter.

There is also another form of protection to think about when you have sex: protection against sexually transmitted diseases (STDs). Some common STDs are HIV/AIDS, chlamydia, genital herpes, gonorrhea, hepatitis, human papilloma virus (HPV), genital warts, syphilis, and trichomonas. Some of these STDs can be very serious and can lead to infertility (inability to have a baby), problems during pregnancy, chronic illness, and even death.

All sexually active women are at risk of catching STDs because they many not know that their partner has an STD (the partner himself may not know). If your partner uses a latex condom correctly each and every time you have sex with him, this will help reduce, but not eliminate, the chance that you will catch an STD.

No other birth control methods will effectively

protect you from STDs. The female condom may give you some STD protection, but it is not as effective as a male latex condom.

For more information on STDs, call the Centers for Disease Control and Prevention (CDC) AIDS/STD Hotline. The CDS phone numbers are 1-800-342-AIDS (2437) for English, 1-800-344-7432 for Spanish, or 1-800-243-7889 for hearing impaired, TDD.

Be sure to protect yourself against pregnancy and STDs by using some form of birth control plus a latex condom. Of course, not having sex is the most effective way to prevent pregnancy and stay free of STDs.

Plan B® One-Step is used to prevent pregnancy after unprotected sex.

Plan B® One-Step should not be used for regular birth control, if you are already pregnant (because it will not work), or if you are allergic to levonorgestrel or any of the ingredients in Plan B® One-Step.

The sooner you take Plan B® One-Step, the better it will work.

Plan B® One-Step does not protect against the AIDS virus (HIV) or other sexually transmitted diseases (STDs)

Common side effects associated with the use of Plan B® One-Step include menstrual changes,

nausea, lower stomach (abdominal) pain, tiredness, headache, dizziness, breast pain and vomiting.		
Duramed Pharmaceuticals, Inc. Subsidiary of Barr Pharmaceuticals, Inc. Pomona, New York 10970 1-800-330-1271 Manufacturer logo ©2009 Duramed Pharmaceuticals, Inc. xxxxxxx	TEVA WOMEN'S HEALTH, INC. A subsidiary of TEVA PHARMACEUTICALS, USA, INC. Sellersville, PA 18960 1-800-330-1271 Manufacturer logo ©2011 Teva Women's Health, Inc. xxxxxxx Month 2011	Company name changed

The proposed deletion is acceptable. The revision to the company name is acceptable.

B. Clinic Carton**i. Outer Carton Label Outside Drug Facts**

Note: The clinic carton is identical to the retail carton except for the following differences. See section II.A.i. for full review and comments.

- a. The statement “For Clinic Use Only. Not For Resale” is located on the top of the PDP.

This is the same as approved, and therefore, is acceptable.

- b. The color scheme of the carton has been changed from green to blue. Unlike the retail carton, the clinic carton does not have any colored accents.

This is acceptable.

ii. Outer Carton Drug Facts Label

Drug Facts on the clinic carton are identical to Drug Facts on the retail carton. See section II.A.ii. for full review and comments.

iii. Immediate Container Label

The immediate container consists of a PVC and aluminum blister, which is attached to the inner panel of the carton.

The sponsor did not provide the immediate container label. Request that the sponsor submit the immediate container (blister card) label for review.

iv. Consumer Information Leaflet (CIL)

The clinic CIL is identical to the retail CIL. See section II.A.iv. for full review and comments.

III. RECOMMENDATIONS

Due to the above-mentioned labeling deficiencies, we cannot recommend approval at this time. We currently recommend a Complete Response action pending the resolution of the following labeling deficiencies:

A. Carton Label Outside Drug Facts (Trade and Clinic Cartons)

1. The statement [REDACTED] (b) (4) is not acceptable. We consider this to be an inappropriate claim for an OTC product. Please remove.
2. We recommend that the strength be listed after the active ingredient name on the PDP to be consistent with other OTC drugs (i.e., “levonorgestrel 1.5 mg”).
3. The phrase [REDACTED] (b) (4)
4. The word “ [REDACTED] (b) (4) ” is not acceptable in the labeling; [REDACTED] (b) (4)
5. The phrase “ [REDACTED] (b) (4) ” is unclear and does not add anything to the approved labeling. We recommend that you use the originally approved language: “One Tablet One Dose” instead of “ [REDACTED] (b) (4) ”.

B. Carton Drug Facts Label (Trade and Clinic Cartons)

6. Moving the [REDACTED] (b) (4)
7. Moving the bulleted statement [REDACTED] (b) (4)
8. A statement indicating that the product is “for women only” needs to be included on the carton or the Drug Facts section of the label. We recommend adding this information as the first bullet under the *Directions* section of Drug Facts.
9. Under the *Other information* heading, [REDACTED] (b) (4)
[REDACTED] The original language should be retained.

10. Remove the period from the end of bulleted statements comprised of only one statement (first and fifth bullets under *Other information*).

C. Consumer Information Leaflet

11. The statement “(b) (4)” is not acceptable. We consider this to be an inappropriate claim for an OTC product. Please remove.
12. The word “(b) (4)” is not acceptable. (b) (4). See comment #4 above.
13. The claim (b) (4) is not acceptable. Replace the first sentence under the subheading “What Plan B One-Step is not” with the previously approved statement: “Plan B One-Step will not work if you are already pregnant and will not affect an existing pregnancy.”
14. The proposed revision under the subheading “How does Plan B One-Step work?” is not acceptable. The original language should be used; however, changing “over 35 years” to “several decades” is acceptable. Change the word “(b) (4)” to “tablet” under this heading when referring to Plan B One-Step.
15. The proposed revision under the subheading “How can I get the best results from Plan B One-Step?” is not acceptable. With exception to changing “a few days” to “72 hours (3 days)” for precision, this section should not be revised. The statement (b) (4)
16. Under the subheading “How will I know (b) (4) Plan B One-Step worked?”, remove the word “(b) (4)” from the subheading and revise the first sentence to read as follows: “You will know Plan B One-Step worked when you get your next period, which should come at the expected time, or within a week of the expected time.”
17. Under the subheading “Will I experience any side effects?”, we recommend bulleted statements to improve clarity and to highlight important information. Move the statement about a missed period to be the first statement since it is important information. Modify this section to read as follows:
- some women may have changes in their period, such as a period that is heavier or lighter or a period that is early or late. **If your period is more than a week late, you maybe pregnant.**
 - if you have severe abdominal pain, you may have and ectopic pregnancy, and should get immediate medical attention
 - when used as directed, Plan B One-Step is safe and effective. Side effects include changes in your period, nausea, lower stomach (abdominal) pain, tiredness, headache, dizziness, and breast tenderness.

- if you vomit within 2 hours of taking the medication, call a healthcare professional to find out if you should repeat the dose”

18. The immediate container (blister card) label was not submitted for review. Please submit the immediate container (blister card) label.

Issue a communication to the sponsor that includes these deficiencies in order to initiate labeling negotiations.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

- a. Carton Label, Clinic.
- b. Carton Label , Trade.
- c. Consumer Leaflet Information

3 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARIA E YSERN
09/29/2011

COLLEEN K ROGERS
09/29/2011

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: September 23, 2011

TO: Melissa Hancock Furness, Regulatory Project Manager
Christina Chang, Medical Officer
Division of Non-Prescription Clinical Evaluation (DNCE)

FROM: Sharon Gershon, Pharm.D.
Good Clinical Practice (GCP) Assessment Branch
Office of Scientific Investigations (OSI)

THROUGH: Susan Thompson, M.D.
Acting Team Leader, GCP Assessment Branch
Office of Scientific Investigations

THROUGH: Jean Mulinde, M.D.
Acting Branch Chief, GCP Assessment Branch
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-998/S-002

APPLICANT: Teva Women's Health Research (formerly Duramed)

DRUG: Plan B[®] 1.5 (levonorgestrel 1.5)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Prevention of pregnancy following unprotected sex, for women
11 – 17 years of age, inclusive

CONSULTATION REQUEST DATE: April 4, 2011

DIVISION ACTION GOAL DATE: December 7, 2011

INSPECTION SUMMARY GOAL DATE: October 7, 2011

I. BACKGROUND:

Plan B® brand of emergency contraceptive pills is indicated for prevention of pregnancy following unprotected intercourse, or after a known or suspected contraceptive failure. Plan B® was approved by FDA on July 28, 1999 for marketing as a prescription product. The original Plan B® regimen consisted of one dose of levonorgestrel 0.75 mg taken as soon as possible within 72 hours after unprotected sex, followed by a second identical dose 12 hours later. A request to switch the product from prescription to over the counter (OTC) status, based on label comprehension and actual use studies, resulted in an approval for OTC sale to consumers aged 18 years and older on August 24, 2006, while maintaining the prescription requirement for women age 17 and younger.

Subsequently, Duramed Research, Inc. (now Teva Women's Health Research) submitted NDA 21-998 for Levonorgestrel 1.5 (referred to as Plan B® 1.5), consisting of a single dose of 1.5 mg levonorgestrel to be taken within 72 hours of unprotected intercourse. On July 10, 2008, the FDA approved this NDA with the trade name of Plan B One-Step®, by prescription for women younger than 17 years old and OTC for consumers 17 years and older.

Teva Women's Health Research (formerly Duramed Research, Inc.) submits NDA 21-998/S-002, which contains data from an Actual Use Study (AUS) to test the ability of women 11-17 years of age to appropriately self-select and correctly use Plan B® 1.5 according to the proposed OTC package label and without provider assistance.

A brief synopsis of the protocol for which the review division has requested clinical investigator inspections is given below.

Protocol DR-LEV-102: Plan B One-Step® Dr-Lev-302: Plan B® 1.5 Emergency Contraception Actual Use Study (AUS) in Adolescents.

The co-primary objectives of this study are to determine the percentage of subjects who appropriately self-selected and the proportion of subjects who correctly used the study product Plan B® 1.5 when dispensed under simulated OTC conditions.

The secondary objectives of this study were to estimate the incidence of adverse events and repeat use of emergency contraception (EC), using a product other than the study product.

This study took place at reproductive health clinics since no one younger than 18 years of age can purchase EC at a pharmacy without a provider prescription. All subjects were screened for eligibility by completion of the Self-Administered Screening questionnaire to record reasons for visiting the clinic, whether they were requesting EC for themselves or someone else, whether they were requesting EC for current or future use, and to assess basic inclusion criteria (e.g., age, previous participation in an EC study, ability to read and understand English, willingness to use the study product without provider assistance, and their willingness and ability to complete study follow-up procedures). Subjects who met the inclusion criteria and who were interested in learning more about the study were provided with additional information and asked to read and sign an IRB-approved Informed Consent Form (ICF).

Confidential and signed informed consent was obtained after the study had been fully explained by study staff (verbally and in writing) at the clinical site. The original signed ICF was retained by the Investigator in the subject's study files at the study site.

To simulate an OTC setting, each potential subject was expected to read the label text on the outside of the study package and determine whether and how to use the study product without provider direction or assistance. The study product, Plan B® 1.5 was to be dispensed only to those subjects who appropriately self-selected **and** indicated that they wanted to participate in the study.

Follow-up contact was conducted by telephone or return clinic visit, at the discretion of the subject and study site. Contact was conducted at approximately one, four, and eight weeks following the date the subject was dispensed study product. At these contacts, subjects answered questions regarding product use, health problems (reported adverse events) since last contact, and pregnancy status. If pregnancy status or the status of any adverse event was not clear at the time of the eight-week contact, additional contacts were to be made at weekly intervals until pregnancy status became clear and/or until all adverse events had resolved or stabilized.

The study was to include a minimum of 300 female subjects who actually used the study product Plan B® 1.5. The first subject was enrolled on October 22, 2008, and the last subject enrolled on November 24, 2010. The study concluded on December 15, 2010.

The review division requested that the confirmation that patient data (particularly adverse events) listed in the Case Report Form matches what is contained in source records (i.e., clinic charts).

II. RESULTS (by Site):

Name of CI, Address	Protocol # and # of Subjects	Inspection Dates	Final Classification
Tina Raine-Bennett, MD Principal Investigator 625 Potrero Avenue New Generation Health Center San Francisco, CA 94110	DR-LEV-302 316 subjects	07/06/2011 – 07/12/2011	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;
EIR has not been received from the field and complete review of EIR is pending.

Tina Raine-Bennett, MD

Principal Investigator
625 Potrero Avenue
New Generation Health Center
San Francisco, CA 94110

On July 5, 2011, Dr. Raine Bennett left New Generation Health Center and began work at Kaiser Permanente, Oakland, CA. Philip D. Darney, M.D., has since taken over as Principal Investigator for this clinical study, and has signed a Form FDA-1572.

- a. **What was inspected:** The inspection was conducted using the clinical investigator compliance program 7348.811, with emphasis on verifying that subject adverse events matched source documents at the clinical site (as requested by the review division). The data listings provided by the Sponsor included Protocol Deviation Log, listing of all Adverse Events, Study Discontinuations, and Enrolled Subjects included in the Study Population for Endpoint Analysis. The FDA field investigator corroborated the Sponsor's data listings with source documentation at the site.

The FDA field investigator:

- Observed how subjects at the site were recruited and enrolled into the study, what constituted a screen failure, and how subjects were deemed to have appropriately self-selected.
- Collected copies of the Subject and Researcher Questionnaires used throughout the study.
- Verified the Listing of Study Discontinuations provided with the assignment for every subject.
- Verified the subjects listed as screen failures (27).
- Reviewed all protocol amendments and ensured they were approved by the IRB prior to implementation.
- Verified that the Protocol Deviation Log submitted with the assignment corroborated with the records at the site for every subject.
- Reviewed all 346 subject ICFs to ensure the correct version was appropriately signed prior to enrolling into the Plan B study.

During the inspection case report forms and source documents were compared to data (line listings) submitted in the NDA for 151 subjects. In addition, drug accountability records, including drug shipment records, accountability logs, drug shipment dates, and drug administration records were reviewed during the inspection.

- b. **General observations/commentary:** The site screened 346 subjects, which was verified during the inspection. The Sponsor reported the number of enrollees as

316, whereas the field investigator noted that there were actually 319 subjects enrolled. The reason for the discrepancy was that three subjects (045, 085 and 340) were screened, confirmed as eligible, and signed an ICD. Two subjects later withdrew, and one subject was taken out of the analysis because of a reported abortion 10 days before signing the ICD. Subject 045 appropriately withdrew from the study because she decided she wanted to talk with someone at the clinic before receiving Plan B (checked NO to question #9 on the Screening Questionnaire). Subject 340 appropriately withdrew from the study because she decided she did not want to give her address or receive phone calls (checked NO to question #8 on the Screening Questionnaire). The EIR states that Subject 085 was pregnant and documentation shows she had an abortion on April 11, 2009. Subject 085 signed the informed consent document to join the study on April 21, 2009, received study drug Plan B, and completed the study. The Sponsor later removed Subject 085 from the analysis. All three of these subjects were considered screen failures by the Sponsor, in addition to the other 27 screen failures. The field investigator verified the 30 screen failures as accurate.

OSI Reviewer Comments: Subject 085 was not pregnant at the time of enrollment, and although she had previously received EC from a clinic (as per documentation), she should still have been permitted to participate in this study. It is not clear why Subject 085 was excluded from the data analysis.

The field investigator compared the Sponsor's data listings with the source data at the site, and found several discrepancies. Specifically, the field investigator found that under the heading "Naïve Product Use", several Subjects (034, 054, 091) should have been listed as "Yes" (had used EC before), whereas they were listed as "No" in the Sponsor's listings.

With respect to adverse events, the field investigator found that all adverse events, except one were accurately reported in the Sponsor's data listings. The exception was Subject 068, who had a reported headache (date not documented in the EIR) that was reported late through a monitor field query.

The field investigator reported that drug accountability records were in good order, and there were no discrepancies.

c. Assessment of data integrity: Several inconsistencies were noted between the Sponsor data listings and source documents. These discrepancies are relatively minor and appear to be isolated occurrences; therefore, it seems unlikely that they would significantly impact NDA analyses. Adverse events were accurately reported, with the exception of one adverse event (headache) that was reported late. With the exception of the items noted above, and the exclusion of Subject 085 from the data analysis, the study appears to have been conducted adequately, and, the data generated by this site may be used in support of the respective indication.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, this study appears to have been conducted adequately and the data in support of the NDA appear reliable. The final classification at the UCSF site was No Action Indicated (NAI), and although a few minor discrepancies were found, the efficacy and safety data for this Actual Use Study are considered reliable.

{See appended electronic signature page}

Sharon K. Gershon, GCP Reviewer
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/s/

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09/23/2011

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09/23/2011



Social Scientist Review
Division of Nonprescription Clinical Evaluation

NDA #: 21-998
Document ID: NDA

Correspondence date: February 7, 2011
Review Date: July 22, 2011
PDUFA Goal Date: December 10, 2011

Sponsor: Duramed Research, Inc.

Drug: Plan B® 1.5 mg

Dosage Form and Route of Administration: Oral Tablet 1.5mg

Active Ingredient(s): Levonorgestrel (1.5mg)

Pharmacologic Category: Contraception

Proposed Indication: Emergency Contraception (EC)

Reviewer: Murewa Oguntimein, MHS, CHES

I. Introduction: This is a social science review of the label comprehension study (LCS) submitted by Duramed Research, Inc. to support a switch from prescription to over-the-counter marketing of levonorgestrel oral tablet (1.5mg) for adolescents younger than 17 years of age.

II. Background:

In July 2009, FDA approved Plan B One-Step for postcoital emergency contraception as an OTC product for women 17 years and older and a prescription product for women younger than 17 years of age. FDA asked the sponsor to provide data relevant to OTC use in younger teens if the sponsor wished to pursue OTC labeling for all women of reproductive age. The sponsor and FDA had a series of interactions to agree on the necessary data, and the label comprehension study (LCS) reviewed here is one of two studies agreed upon to support OTC labeling in younger teens. The other study, an Actual Use Study (AUS), is reviewed by Dr. Christina Chang in the clinical review of the current submission.

On April 19, 2007, Duramed submitted a meeting background package containing their proposed studies in adolescents (label comprehension study; “**Plan B 1.5[®] Emergency Contraception Label Comprehension Study**” and an actual use study; “**Plan B[®] Emergency Contraception Actual Use Study**”) that they planned to conduct to remove the Rx requirement for Plan B® 1.5 for women age 17 and under. FDA conducted a review of the proposed studies and comments were sent to the Sponsor. On August 7, 2007, Duramed submitted a justification for excluding 11-year-olds in the label comprehension study because this age group was unlikely to need or purchase the Plan B 1.5 drug product. Duramed started the label comprehension study prior to receiving the agency’s response on October 22, 2007.

On December 21, 2007 the Agency responded to Duramed's justification in writing. After internal discussions that included the director of CDER, Dr. Stephen Galson, the Agency stated "that a minimum of 50 subjects in each age group (12, 13, 14, 15, 16, and 17 year olds) should be enrolled. Those who are under age 12 years who are eligible to participate should be tested and factored into the final analysis. You will not be held to a minimum enrollment for subjects under 12 years of age." The following additional comments and recommendations were provided by the Agency:

- Changes made to your proposed label comprehension study, study questionnaire, draft label, and Statistical Analysis Plan appear to be acceptable. Ultimately, the assessment as to whether or not subjects understand the key concepts will be a review issue.
- Technically there is not a 'two-sample proportion t-test'. Your analysis plan should be more specific about the particular test to be used.
- You state that "No formal statistical analysis of these verbatim responses will be undertaken, and they will not be used to alter the participant's initial response to the question." Verbatim responses should be coded and analyzed. Adjustments should be made when the verbatim answer clearly demonstrates that the subject 'guessed' the correct answer.

Duramed revised the protocol in accordance with the above recommendations, and continued recruitment of subjects. FDA found the revised protocol acceptable. The label comprehension study was conducted between October 22, 2007 and February 8, 2008.

The final study report for the label comprehension study titled "**Plan B[®] 1.5 Emergency Contraception Label Comprehension Study**" was submitted on February 7, 2011 as part of the sNDA. The following is a review of the study and study results.

III. LABEL COMPREHENSION STUDY:

A. Title: Plan B[®] 1.5 Emergency Contraception Label Comprehension Clinical Study (#10025)

B. Purpose: To evaluate whether young women aged 12-17 years could understand the information needed for safe and effective use of Plan B[®] 1.5 by reading a sealed box with a prototypical OTC label printed on the outside front and back panels.

C. Objectives:

Primary objectives:

The primary objectives were to measure in young women aged 12-17 years inclusive, comprehension of each of the three key primary concepts:

1. Plan B[®] 1.5 is indicated for prevention of pregnancy after unprotected sex.
2. Plan B[®] 1.5 should be taken as soon as possible after sex.
3. Plan B[®] 1.5 does not prevent sexually transmitted diseases or HIV/AIDS.

Secondary objectives:

The secondary objectives were to measure, in young women aged 12-17 years inclusive, comprehension of each of the three key secondary concepts:

4. Plan B® 1.5 should not be used in place of regular contraception.
5. Plan B® 1.5 should be taken within 72 hours after sex.
6. Plan B® 1.5 should not be used by women who are already pregnant.

No target thresholds for the primary and secondary objectives were set.

Reviewer's Comments

The primary and secondary objectives for this study appear to be acceptable.

It is also acceptable that target thresholds were not set for these objectives, since an actual use study with this particular population (young women aged 12-17 years, inclusive) was also conducted and the label development was an iterative process to ensure that the best label was used in the actual use study.

D. Study Design: This was a multi-site, open-label, single-visit targeted label comprehension study. It took place at shopping malls and clinics in eight metropolitan areas across the United States. These areas were: Atlanta, GA, Chicago, IL, Denver CO, Los Angeles, CA, Miami, FL, Philadelphia, PA, East St. Louis, IL, and Seattle, WA. Mall recruitment occurred at all sites. Clinic recruitment occurred in family planning clinics in all areas except Atlanta, Los Angeles, and St. Louis.

All data collected from the sites in Chicago and Miami were excluded from the analysis due to research misconduct that was discovered in November, 2007. The sponsor discovered handwriting irregularities on data forms from Chicago and Miami. Further investigation revealed that unauthorized, untrained personnel completed data forms at these two sites, and then authorized, trained site staff signed the forms. Therefore, the decision was made to exclude 67 eligible subjects that were enrolled at these two sites. The sponsor then reviewed data forms from the remaining sites, and did not discover misconduct at these sites. Subject recruitment targets at the remaining six sites were increased to compensate for the exclusion of subjects from the Chicago and Miami sites. Table 1 provides a list of the study sites with the number of subjects recruited, eligible and who completed (answered all questions about the label) the study (see Table 1).

Table 1. Number of Subjects Recruited, Eligibility, and Completed by City

	Study Sites						
	Atlanta	Denver	LA	Philadelphia	East St. Louis	Seattle	Total
<u>Recruitment Site</u>							
Mall	57	46	92	41	64	32	332
Clinic	0	8	0	20	0	17	45
Eligibility	55	53	69	56	56	46	335
Completed (answered all qxn about label)	55	51	64	56	56	45	327

Table adapted from Sponsor's Table 1.1 (Page 1 of Appendix 9 of study report)

Reviewer's Comments

The exclusion of data collected from the Chicago and Miami sites appears to be acceptable because the data collected deviated from the study protocol procedures. Although these two study sites were excluded the sponsor was able to meet the enrollment requirement.

The research sites and number of subjects enrolled and those who completed the study from these sites appear to be adequate.

a. Recruitment-Screening

Potential subjects were screened in the shopping malls and family planning clinics. Eligible subjects who expressed interest in participating in the study were taken to the interview office in the mall setting or to an isolated room or area in the clinic setting if they met the following inclusion/exclusion criterion:

b. Inclusion criteria:

- Consent had been obtained from the subject.
- Consent from the parent or guardian had been obtained if the subject was aged 14 or younger and was interviewed in the mall setting.
- Subject was female and aged 12-17 years, inclusive.
- Subject claimed to read and understand English.
- Subject was comfortable being interviewed in English;
- Subject had not participated in a study about any medication package, by her report.

c. Exclusion criteria:

- Subject did not provide consent.
- The parent or guardian did not provide consent if the subject was aged 14 or younger and was interviewed in the mall setting.
- Subject was male.
- Subject was female and was not aged 12-17 years, inclusive.
- Subject claimed not to be able to read and understand English.
- Subject was not comfortable being interviewed in English;
- Subject had previously participated in a study about any medication package or appeared to know the topic of the study.

d. Study Procedure:

Female interviewers asked the study subjects questions to confirm that the subjects provided consent and met the study eligibility criteria. The information collected was documented in the study database. After the data was documented, the Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen) test was administered to all subjects to screen for literacy levels. Subjects with a REALM-Teen test score of 58 or lower were categorized as low literate and subjects with a score 59 and above were categorized as normal literate. A score of 58 or lower correspond to a 7th grade reading level or lower and a score of 59 corresponds to a 8th grade or above reading level.

Subjects were given the sealed prototype Plan B® 1.5 package and asked to read and review the outside front and back package label (See appendix A), and then the interviewer administered the label comprehension questionnaire to the subjects. The interview consisted of closed-ended scenario-based and open-ended questions. The close-ended options included: “yes,” “no,” “don’t know,” and “no response given.” These questions were related to the correct and incorrect use of the product according to the information on the package. All subjects were asked a follow-up “Why do you say that” question after some of the comprehension questions to better understand their initial response (See appendix B). Subjects were also permitted to refer to the package label while answering these questions, mimicking the likely conditions of actual product use.

A specific set of 19 questions was designed to test understanding of the six key concepts (three primary and three secondary concepts). Four questions were developed for concept 1, four for concept 2, two

for concept 3, and three each for concepts 4, 5, and 6. Most of these 19 total questions described scenarios that required the subject to consider whether or not use of the product would be appropriate in a particular situation, according to the package label (see appendix C). The subject was considered to have demonstrated understanding of a concept if she provided correct responses to a pre-specified number of the questions that mapped to that concept. The understanding of each concept was evaluated independently. The following table is the number of questions related to each concept and the minimum number of correct responses needed to demonstrate understanding of that specific concept:

Table 2. Summary of Key Concepts and Questions Demonstrating Understanding

Key Concepts	Number of Questions Asked	Correct Responses needed to Demonstrate Understanding of Key Concepts
Primary Objectives		
1. Plan B® 1.5 is indicated for prevention of pregnancy after unprotected sex.	4	3
2. Plan B® 1.5 should be taken as soon as possible after sex.	4	3
3. Plan B® 1.5 does not prevent sexually transmitted diseases or HIV/AIDS.	2	2
Secondary Objectives		
4. Plan B® 1.5 should not be used in place of regular contraception.	3	2
5. Plan B® 1.5 should be taken within 72 hours after sex.	3	2
6. Plan B® 1.5 should not be used by women who are already pregnant.	3	2

Table from Sponsor (Page 11 of study report)

Reviewer’s Comments

The screening script, consent form, drug facts label, and interview scripts were provided in the submission. The screening script, consent form, and interview script do not appear to provide information that could have potentially biased the study. These appear to be acceptable.

Based on subjects’ responses, one of the questions supporting Key Concept #2 appeared to be confusing and may have contributed to lower scoring of that concept (79% correct). The scenario-based question was as follows:

[REDACTED] (b) (4)

Per protocol, the correct answer was “Thursday night”; however, the question is ambiguous. A better question would have been “when was the best time to buy it and take it.” The data show that some subjects chose “Saturday” or “it doesn’t matter” because Saturday was as soon as Ellie could have taken the product given the time of purchase. These subjects explained their choice with “It works best if used ASAP,” “the sooner the better,” “b/c she should have bought it before,” and “because that’s when she bought it.” Although these subjects chose a response that was incorrect per protocol, they appear to have understood the concept. Among those subjects who answered “Saturday” as the best time to take the product, 81% (43/53) indicated that the reason they chose that day was because it was within the 72

hours (three days) limit that was written on the box. In addition, 10 out of the 19 subjects who answered “Doesn’t matter” also indicated that the reason they chose “Doesn’t matter” was because the two options “Thursday” and “Saturday” are both within the 72 hours (three days) limit that was written on the box. Subjects performed better on a clearer question testing Key Concept #2:

(b) (4)

“Right away” was chosen by 87.2% of subjects.

The method of calculating subjects’ understanding of each key concept appears to be acceptable since adolescents may find it difficult to articulate the reason why they responded to some questions the way they did.

After the label comprehension study was completed, the interviewers collected additional information regarding the study subjects’ demographics, educational level and their parents’ education level. Finally, subjects completed a self-administered questionnaire regarding their sexual and contraceptive experience including sexual education and previous exposure to and/or use of emergency contraceptive pills (ECPs). This information was collected in order to ensure a diverse population of females and females who had not previously used EC were included in the study.

Reviewer’s Comments

FDA recommended, and the sponsor agreed to include, minimum quotas of race, ethnicity, literacy, and no prior EC use to provide an adequate sampling of the U.S. population. The quotas for race and ethnicity were based on U. S. census data from the year 2000; the quota for literacy was based on the 2002 National Assessment of Adult Literacy.

E. Study Population: The study consisted of 335 female subjects between the ages of 12-17 years inclusive. Each age group included between 54 and 59 subjects with age group 15 having the largest number of subjects (59) and age groups 12 and 14 having the smallest number of subjects (54). Forty-two percent (140/335) of the study population were low literate and 58.2% (195/335) were normal literate. Over half of the study population was white females with an age distribution of 12-17 (58.8%). A small percentage of subjects reported ever previously using emergency contraceptive pills (ECPs) (7%; 24/335). No subjects aged 11 years or younger were enrolled. The demographics of the sample are summarized in Table 3.

Table 3. Respondent Demographics

Demographics	Total	%
Age (years)	335	
12	54	16.1
13	56	16.7
14	54	16.1
15	59	17.6
16	57	17.0
17	55	16.4
Race*		
Caucasian	197	58.8
African American	88	26.3
Asian or Pacific Islander	4	1.2
American Indian/Alaska Native	7	2.1
Other	71	21.2
More than one race	37	11.0
Don't know	0	0
No response given	2	0.6
Missing	8	2.4
Hispanic Origin		
Hispanic	70	20.9
Non-Hispanic	254	75.8
Don't Know	3	0.9
No response given	0	0
Missing	8	2.4
Literacy		
Normal Literacy	195	58.2
Low Literacy	140	41.8
Previous ECP Use		
Yes	24	7.2
No	127	37.9
Missing	184	54.9
*Multiple answers allowed		

Table adapted from Sponsor (Page 3, 6 and 10 of Appendix 9 of study report)

Reviewer's Comments

The demographics of the subjects in this study appear to be a reasonable representation of the U.S. population.

The number of subjects appears to be acceptable since they were based on the agency's recommendation to enroll at least 300 female subjects, 50 of each age 12-17 years, inclusive in the study.

F. Results: The results are divided into five categories: (1) A table of the Understanding of all Key Concepts (Primary and Secondary Objectives) (2) A table of the Understanding of all Key Concepts- comparison by Literacy level (3) A table of the Understanding of all Key Concepts- comparison by Age (4) A table of the Understanding of all Key Concepts comparison by prior use of Emergency Contraceptive Pills. The results were as follows:

1. Table 4 depicts the number and percent of subjects who correctly answered the questions related to the primary objectives and the secondary objectives. The results indicate that majority of the subjects comprehended the key concepts in the Plan B® 1.5 package label (82.7%-95.5%). It should be noted that amongst the primary objectives key concept 3 (Plan B® 1.5 does not prevent sexually transmitted diseases or HIV/AIDS) was the most understood concept (92.5%) and key concept 2 (Plan B® 1.5 should be taken as soon as possible after sex) was the least understood (82.7%). Amongst the secondary objectives key concept 6 (Plan B® 1.5 should not be used by women who are already pregnant) was the most understood concept (95.5%) and key concept 4 (Plan B® 1.5 should not be used in place of regular contraception) was the least understood (92.2%). Table 4 below summarizes these results.

Table 4. Understanding of All Key Concepts (Primary and Secondary Objectives)

Key Concepts	Subjects with Correct Understanding	% of Subjects with Correct Understanding	95% C.I. of the Correct Understanding
Primary Objectives			
1. Plan B® 1.5 is indicated for prevention of pregnancy after unprotected sex.	300	89.6	(85.8,92.6)
2. Plan B® 1.5 should be taken as soon as possible after sex.	277	82.7	(78.2, 86.6)
3. Plan B® 1.5 does not prevent sexually transmitted diseases or HIV/AIDS.	310	92.5	(89.2,95.1)
Secondary Objectives			
4. Plan B® 1.5 should not be used in place of regular contraception.	309	92.2	(88.8,94.9)
5. Plan B® 1.5 should be taken within 72 hours after sex.	319	95.2	(92.4, 97.2)
6. Plan B® 1.5 should not be used by women who are already pregnant.	320	95.5	(92.7,97.5)

Table adapted from Sponsor's table 5.1a (Page 121 of Appendix 9 of study report)

Reviewer's Comments

The results of the correct understanding of the primary objectives (1-3 key concepts) and the secondary objectives (4-6 key concepts) appear to be adequate.

Even though concept 2(Plan B® 1.5 should be taken as soon as possible after sex) was the most misunderstood concept (277/335; 82.7%) Concept 5 (Plan B® 1.5 should be taken within 72 hours after sex) was understood by the vast majority (319/335;95.2%) which implies that adolescents understood that

the product should be taken within 72 hours after sex, which is acceptable but not ideal; the sooner the consumer takes the product the more effective it is. The proposed labeling is slightly changed from the label used in the study and the changes appear to “call out” the concept of taking Plan B One-Step as soon as possible. The following statements appear prominently on the proposed packaging: (b) (4)

“The sooner you take it, the more effective it will be.” “Take as soon as possible within 72 hours (3 days) after unprotected sex.”

2. Table 5 depicts the number and percentage of respondents who correctly answered the questions related to the primary objectives and the secondary objectives by literacy level. There was a moderate comprehension rate among the low literate group ranging from 74.3% to 92.1%. It should be noted that when compared to the normal literate group, the lower literate group comprehended less than their normal literate counterparts. The following is a range of percentages between both groups (normal literate vs. low literate) of respondents corresponding to the key concepts (primary and secondary objectives):

1. Plan B® 1.5 is indicated for prevention of pregnancy after unprotected sex: 94.9% vs. 82.1%
2. Plan B® 1.5 should be taken as soon as possible after sex: 88.7% vs. 74.3%
3. Plan B® 1.5 does not prevent sexually transmitted diseases or HIV/AIDS: 98.5% vs. 84.3%
4. Plan B® 1.5 should not be used in place of regular contraception: 95.9 % vs. 87.1%
5. Plan B® 1.5 should be taken within 72 hours after sex: 97.4% vs. 92.1%
6. Plan B® 1.5 should not be used by women who are already pregnant: 97.7% vs. 92.1%

Table 5. Understanding of All Key Concepts by Literacy Level¹

Key Concepts	Literacy level		Total
	Low Literacy	Normal Literacy	
	N= 140	N = 195	N= 335
	n (%)	n (%)	n (%)
Primary Objectives			
1. Plan B® 1.5 is indicated for prevention of pregnancy after unprotected sex.	115 (82.1)	185 (94.9)	300 (89.6)
2. Plan B® 1.5 should be taken as soon as possible after sex.	104 (74.3)	173 (88.7)	277 (82.7)
3. Plan B® 1.5 does not prevent sexually transmitted diseases or HIV/AIDS.	118 (84.3)	192 (98.5)	310 (92.5)
Secondary Objectives			
4. Plan B® 1.5 should not be used in place of regular contraception.	122 (87.1)	187 (95.9)	309 (92.2)
5. Plan B® 1.5 should be taken within 72 hours after sex.	129 (92.1)	190 (97.4)	319 (95.2)
6. Plan B® 1.5 should not be used by women who are already pregnant.	129 (92.1)	191 (97.9)	320 (95.5)

¹ REALM-Teen score: 0-58= 7th or lower; lower literacy, 59-66= 8th grade or higher
Table from Sponsor’s table 5.1g (page 127 of Appendix 9 of study report)

Reviewer’s Comments

Even though some of subjects in the low literate group did not understand concept 2 (Plan B® 1.5 should be taken as soon as possible after sex) (104/140; 74.3%), most of them understood concept 5 (Plan B® 1.5 should be taken within 72 hours after sex) (129/140; 92.1%) which implies that the low literate group understood that product should be taken within 72 hours after sex. This result is acceptable because

there is reasonable, though less, effectiveness, when Plan B One-Step is taken at 72 hours. Based on experience with other LCS, this slightly lower understanding among low literates is expected.

3. Table 6 depicts the number and percents of respondents who correctly answered the questions related to the primary objectives and the secondary objectives by age. The results indicate that most subjects in the age group 12-17 comprehended the key concepts (primary and secondary objectives) (76.8%-98.2%). It should be noted that the subjects in age group 13 comprehended the least as compared to the other age groups 12, 14, 15, 16, and 17 for key concepts 1, 2, and 4:

1. Plan B® 1.5 is indicated for prevention of pregnancy after unprotected sex: 82.1 vs. 87.0%, 85.2%, 94.9%, 91.2%, 96.4%)
2. Plan B® 1.5 should be taken as soon as possible after sex: 76.8% vs. 77.8%, 83.3%, 88.1%, 82.5%, 87.3%)
4. Plan B® 1.5 should not be used in place of regular contraception: 87.5%, vs. 92.6 %, 90.7%, 93.2%, 93.0%, 96.4%)

In addition, subjects in age group 14 comprehended the least as compared to the other age groups 12, 13, 15, 16, and 17 for key concepts 3, 5, and 6. (Age group 14 ; 87.5%, 88.9%, 90.7% vs. age group 12; 90.7%, 98.1%, 94.4%, age group 13; 87.5%, 89.3%, 94.6% age group 15; 98.3%, 98.3% 98.3% age group 16; 94.7%, 98.2%, 96.5% and age group 17;96.4%,98.2%, 98.2%). Table 6 below summarizes these results.

Table 6. Understanding of All Key Concepts by Age

Key Concepts	Age						Total
	12	13	14	15	16	17	
	N= 54 n (%)	N= 56 n (%)	N= 54 n (%)	N= 59 n (%)	N= 57 n (%)	N= 55 n (%)	
Primary Objectives							
1. Plan B® 1.5 is indicated for prevention of pregnancy after unprotected sex.	47 (87.0)	46 (82.1)	46 (85.2)	56 (94.9)	52 (91.2)	53 (96.4)	300 (89.6)
2. Plan B® 1.5 should be taken as soon as possible after sex.	42 (77.8)	43 (76.8)	45 (76.8)	52 (88.1)	47 (82.5)	48 (87.3)	277 (82.7)
3. Plan B® 1.5 does not prevent sexually transmitted diseases or HIV/AIDS.	49 (90.7)	49 (87.5)	47 (87.0)	58 (98.3)	54 (94.7)	53 (96.4)	310 (92.5)
Secondary Objectives							
4. Plan B® 1.5 should not be used in place of regular contraception.	50 (92.6)	49 (87.5)	49 (90.7)	55 (93.2)	53 (93.0)	53 (96.4)	309 (92.2)
5. Plan B® 1.5 should be taken within 72 hours after sex.	53 (98.1)	50 (89.3)	48 (88.9)	58 (98.3)	56 (98.2)	54 (98.2)	319 (95.2)
6. Plan B® 1.5 should not be used by women who are already pregnant.	51 (94.4)	53 (94.6)	49 (90.7)	58 (98.3)	55 (96.5)	54 (98.2)	320 (95.5)

Table from Sponsor's table 5.1d (page 124 of Appendix 9 of study report)

Reviewer's Comments

The results of the correct understanding to the primary and secondary objectives amongst the ages appear to be reasonable because it is similar across age groups. There does not appear to be a large drop in understanding among the younger subjects. The correct response rate ranged from 76.8% - 98.2%.

4. Table 7 depicts the number and percent of subjects who correctly answered the questions related to the key concepts (primary and secondary objectives) by prior use of ECPs. The result indicates that subjects who had used ECPs comprehended the key concepts 1, 3, 5 and 6 somewhat better than the subjects who had never used ECPs:

1. Plan B® 1.5 is indicated for prevention of pregnancy after unprotected sex: 100% vs. 88.7%
3. Plan B® 1.5 does not prevent sexually transmitted diseases or HIV/AIDS: 100% vs. 92.0%
5. Plan B® 1.5 should be taken within 72 hours after sex: 100% vs. 94.9%
6. Plan B® 1.5 should not be used by women who are already pregnant: 100% vs. 95.2%

Table 7. Understanding of All Key Concepts by Ever Use of Emergency Contraceptive Pills¹ (ECPs)

Key Concepts	EC use		Total
	Prior use	Never use	
	N= 24 n (%)	N= 311 n (%)	N= 335 n (%)
Primary Objectives			
1. Plan B® 1.5 is indicated for prevention of pregnancy after unprotected sex.	24 (100.0)	276 (88.7)	300 (89.6)
2. Plan B® 1.5 should be taken as soon as possible after sex.	20 (83.3)	257 (82.6)	277 (82.7)
3. Plan B® 1.5 does not prevent sexually transmitted diseases or HIV/AIDS.	24 (100.0)	286 (92.0)	310 (92.5)
Secondary Objectives			
4. Plan B® 1.5 should not be used in place of regular contraception.	23 (95.8)	286 (92.0)	309 (92.2)
5. Plan B® 1.5 should be taken within 72 hours after sex.	24 (100.0)	295 (94.9)	319 (95.2)
6. Plan B® 1.5 should not be used by women who are already pregnant.	24 (100.0)	296 (95.2)	320 (95.5)

¹Subjects who did not report use of ECPs are counted as never having used them.
Table from Sponsor's table 5.1h (page 128 of Appendix 9 of study report)

Reviewer's Comments

It is not surprising that subjects with prior experience using ECPs had a slightly better comprehension of several key concepts than those who had never used ECPs.

The fact that the subjects who did not report use of ECPs were counted as never having used them, may account for the small number of subjects in the "prior use" group because some of these subjects may actually have used the product previously.

IV. Discussion

Overall, this was a very thorough, well-designed label comprehension study with the adequate sample size between age 12-17 inclusive. The study achieved pre-specified objectives by estimating the proportion of young women aged 12-17 years, inclusive, who demonstrate an understanding of six key concepts of OTC labeling. Most subjects comprehended the six key concepts (82.7%-95.5%), with key concept 2 (Plan B® 1.5 should be taken as soon as possible after sex) being the least

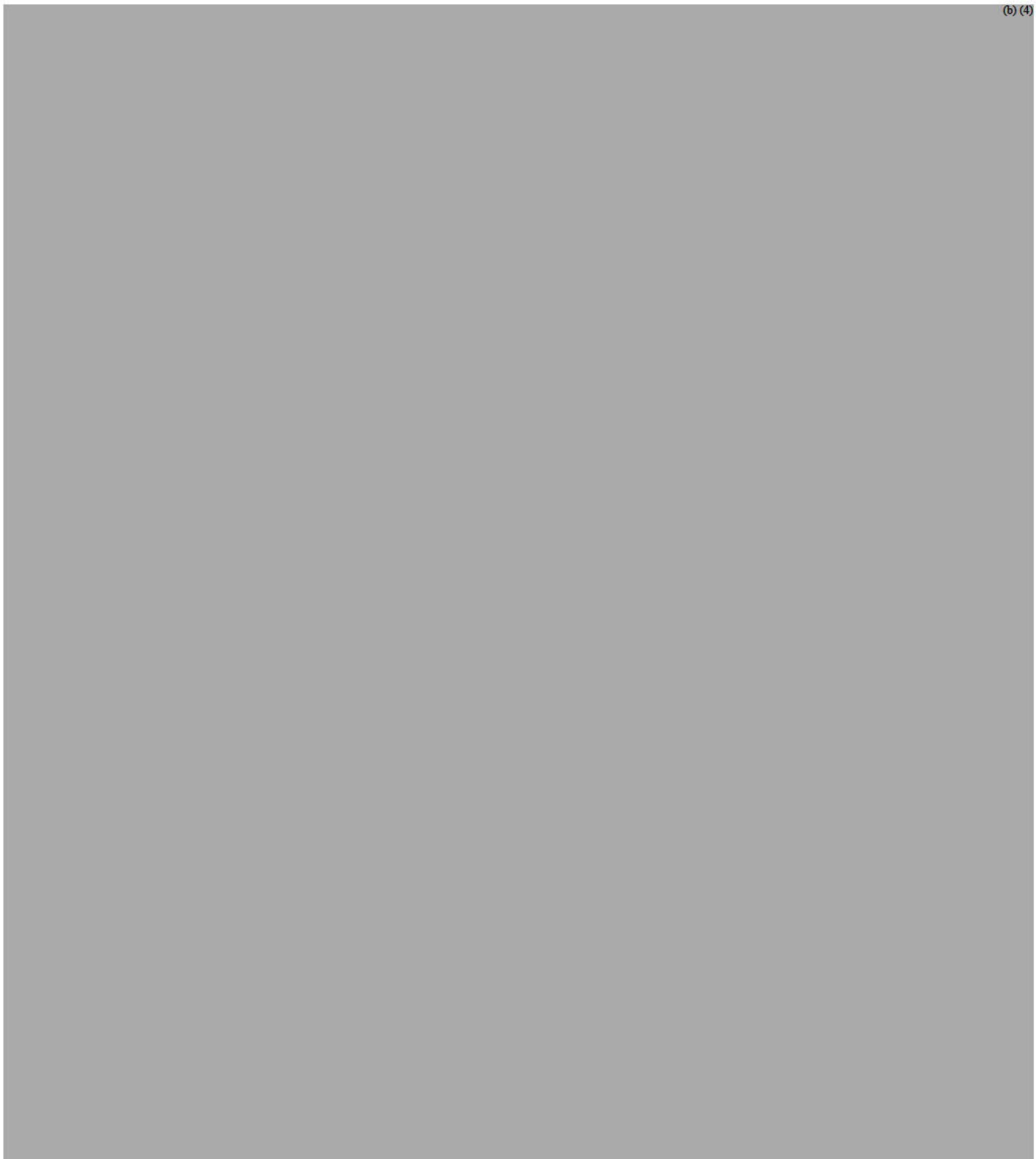
understood; however, efficacy should be acceptable because the related concept, take within 72 hours, was very well understood (95.2%). In addition, most subjects in the low literate group (74.3% - 92.1%) comprehended the six key concepts. This study only evaluates how well subjects recruited in shopping malls and family planning clinics understand certain labeling elements; this study does not evaluate how actual users of the product will behave. For this NDA supplement, the sponsor performed an actual use study that is under review by the clinical team.

V. Conclusion

The study demonstrated that adolescents were able to understand the key elements of the label. The approval of this NDA supplement will also depend on how well the label translates to safe and appropriate use of the product in the actual use study, which will be determined by the evaluation of the actual use study.

The labeling elements tested are acceptable based on the results of this study. In the proposed label, the sponsor has added prominent text to emphasize the importance of taking the product as soon as possible; this is acceptable.

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page



4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

OLUWAMUREWA OGUNTIMEIN
07/25/2011

LESLEYANNE A FURLONG
07/25/2011
I concur.

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 021998	NDA Supplement #:S- 002	Efficacy Supplement Type SE- 5
Proprietary Name: Plan B [®] One-Step Established/Proper Name: levonorgestrel Dosage Form: tablets Strengths: 1.5 mg		
Applicant: Teva Women's Health, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: February 7, 2011 Date of Receipt: February 7, 2011 Date clock started after UN: N/A		
PDUFA Goal Date: December 7, 2011	Action Goal Date (if different):	
Filing Date: April 8, 2011	Date of Filing Meeting: March 31, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) N/A		
Proposed indication(s)/Proposed change(s): This supplemental application proposes to expand the existing nonprescription patient population to allow for the nonprescription availability of Plan B [®] One-Step for all women of child-bearing potential.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		Note: firm originally submitted as a (b)(2), however, it was determined the clinical literature submitted was not essential for approval by the Clinical team and after discussions with the ADRA and OND IO TL, it was determined that this should be a (b)(1) application.
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other: Expansion of OTC patient population	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number(s):				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 3</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?				
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p>PREA</p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>				

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>			X	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/DCRMS via the DCRMSRMP mailbox</i>			X	
Prescription Labeling	<input checked="" type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>			X	
Is the PI submitted in PLR format? ⁴			X	

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?			X	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)				
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?			X	
OTC Labeling	<input type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Outer carton label <input checked="" type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input checked="" type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	X			
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	X			
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>			X	
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>				

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: 03-31-11

BLA/NDA/Supp #: 21-998/S-002

PROPRIETARY NAME: Plan B[®] One-Step

ESTABLISHED/PROPER NAME: levonorgestrel

DOSAGE FORM/STRENGTH: tablets, 1.5 mg

APPLICANT: Teva Women's Health, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): This supplemental application proposes to expand the existing nonprescription patient population to allow for the nonprescription availability of Plan B[®] One-Step for all women of child-bearing potential.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Melissa Furness	Y
	CPMS/TL:	Melissa Furness	Y
Cross-Discipline Team Leader (CDTL)	Lesley Furlong		Y
Clinical	Reviewer:	Christina Chang	Y
	TL:	Lesley Furlong	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	Murewa	N
	TL:	Lesley Furlong	Y
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	Maria Ysern	Y
	TL:	Colleen Rogers	Y
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:		
	TL:		
Biostatistics	Reviewer:	Rima Izem	Y
	TL:	Yan Wang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:		
	TL:		
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:		
	TL:		
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	Andrea Leonard- Segal, Director, DNCE; Joel Schiffenbauer, Deputy Director, DNCE; Charles Ganley, Director, ODE IV; Shaw Chen, Deputy Director, ODE IV		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined
<i>If no, for an original NME or BLA application, include the</i>	Reason:

<p><i>reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: IR sent and response from Sponsor received from sponsor prior to filing that avoided RTF.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
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<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Andrea Leonard-Segal, M.D., M.S.	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

<input type="checkbox"/>	<ul style="list-style-type: none"> • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MELISSA H FURNESS
05/25/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021998/S-002

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 021998

SUPPL # 002

HFD # 560

Trade Name Plan B One-Step

Generic Name levonorgestrel

Applicant Name Teva Branded Pharmaceutical Products R&D, Inc.

Approval Date, If Known *See AP Letter Signature Date*

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES

NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

SE6 (Rx to OTC for ages 15-17)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES

NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Extension of the OTC population from minimum age 17 years to minimum age 15 years.

d) Did the applicant request exclusivity?

YES

NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three

e) Has pediatric exclusivity been granted for this Active Moiety?

YES

NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES

NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES

NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21045

Plan B

NDA# 21998

Plan B One-Step

A complete list of approved OTC and Rx products containing levonorgestrel is attached to the end of this form. There are 7 listed OTC products, including the two NDAs listed above, and there are over 30 listed Rx products containing levonorgestrel alone or in combination with other drugs.

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

N/A

YES

NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s). ***Please see above.***

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

DR-LEV-302, "Plan B 1.5 Emergency Contraception Actual Use Study"

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO
(DR-LEV-302, "Plan B 1.5 Emergency Contraception Actual Use Study")

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

DR-LEV-302, "Plan B 1.5 Emergency Contraception Actual Use Study"

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

!

IND # 74294

YES

!

! NO

! Explain:

IND managed by DNCE.

Investigation #2

!

IND #

YES

!

! NO

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

! Not applicable, was done under an IND.

NDA 21998 S-002

YES
Explain:

!
! NO
! Explain:

Investigation #2

YES
Explain:

!
!
! NO
! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Doris J. Bates, Ph.D.
Title: Senior Regulatory Project Manager / Safety Regulatory Project Manager,
Division of Nonprescription Clinical Evaluation
Date: See DARRTS signature block.

Name of Office/Division Director signing form: Shaw T. Chen, M.D., Ph.D.
Title: Director (Acting)
Division of Nonprescription Clinical Evaluation
Date: See DARRTS signature block.

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12



U.S. Food & Drug Administration

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

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 2
 3
 FDA Home

Active Ingredient Search Results from "OB_Rx" table for query on "Levonorgestrel."

Appl No	TE Code ⁴	RLD ⁵	Active Ingredient	Dosage Form; Strength Route	Proprietary Name	Applicant
N021258		Yes	ESTRADIOL; LEVONORGESTREL	FILM, EXTENDED RELEASE; TRANSDERMAL 0.045MG/24HR;0.015MG/24HR	CLIMARA PRO	BAYER HLTHCARE
A091674	AB	No	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL 0.02MG,0.01MG;0.1MG,N/A	LEVONORGESTREL AND ETHINYL ESTRADIOL	LUPIN LTD
A091440	AB	No	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL 0.03MG;0.15MG	LEVONORGESTREL AND ETHINYL ESTRADIOL	LUPIN LTD
A079064	AB	No	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL 0.03MG;0.15MG	INTROVALE	SANDOZ
N022262	AB	No	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL 0.02MG,0.01MG;0.1MG,N/A	LOSEASONIQUE	TEVA BRANDED PHARM
N021840	AB	Yes	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL 0.03MG,0.01MG;0.15MG,N/A	SEASONIQUE	TEVA BRANDED PHARM
N021544	AB	Yes	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL 0.03MG;0.15MG	SEASONALE	TEVA BRANDED PHARM
A200407	AB	No	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL 0.02MG,0.01MG;0.1MG,N/A	LEVONORGESTREL AND ETHINYL ESTRADIOL	WATSON LABS
A079218		Yes	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL 0.02MG;0.09MG	LEVONORGESTREL AND ETHINYL ESTRADIOL	WATSON LABS
A078834	AB	No	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL 0.03MG,0.01MG;0.15MG,N/A	LEVONORGESTREL AND ETHINYL ESTRADIOL AND ETHINYL ESTRADIOL	WATSON LABS
A077101	AB	No	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL 0.03MG;0.15MG	QUASENSE	WATSON LABS
A075803	AB2	No	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL- 28 0.02MG;0.1MG	LESSINA-28	BARR
A075866	AB	No	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL- 28 0.03MG;0.15MG	PORTIA-28	BARR
A075796	AB1	No	ETHINYL ESTRADIOL;	TABLET; ORAL- 28 0.02MG;0.1MG	AVIANE-28	DURAMED PHARMS

LEVONORGESTREL				BARR		
A075809	AB	No	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL- 0.03MG,0.04MG,0.03MG;0.05MG,0.075MG,0.125MG ENPRESSE-28 28	DURAMED PHARMS BARR	
A091663	AB	No	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL- 0.03MG;0.15MG 28	LEVONORGESTREL AND ETHINYL ESTRADIOL	FAMY CARE LTD
A091452	AB	No	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL- 0.03MG;0.15MG 28	MARLISSA	GLENMARK GENERICS
A091425	AB1	No	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL- 0.02MG;0.1MG 28	LEVONORGESTREL AND ETHINYL ESTRADIOL	LUPIN LTD
A091408	AB	No	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL- 0.03MG;0.15MG 28	KURVELO	LUPIN LTD
A090721	AB1	No	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL- 0.02MG;0.1MG 28	FALMINA	NOVAST LABS LTD
A090719	AB	No	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL- 0.03MG,0.04MG,0.03MG;0.05MG,0.075MG,0.125MG LEVONEST 28		NOVAST LABS LTD
A079102	AB	No	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL- 0.03MG;0.15MG 28	ALTAVERA	SANDOZ
N018782	AB	Yes	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL- 0.03MG;0.15MG 28	NORDETTE-28	TEVA BRANDED PHARM
A077099	AB1	No	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL- 0.02MG;0.1MG 28	ORSYTHIA	VINTAGE PHARMS LLC
A077502	AB	No	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL- 0.03MG,0.04MG,0.03MG;0.05MG,0.075MG,0.125MG MYZILRA 28		VINTAGE PHARMS LLC
A076625	AB1	Yes	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL- 0.02MG;0.1MG 28	LEVONORGESTREL AND ETHINYL ESTRADIOL	WATSON LABS
A077681	AB2	Yes	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL- 0.02MG;0.1MG 28	LEVONORGESTREL AND ETHINYL ESTRADIOL	WATSON LABS
A074538	AB	Yes	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL- 0.03MG,0.04MG,0.03MG;0.05MG,0.075MG,0.125MG TRIVORA-28 28		WATSON LABS
A073594	AB	No	ETHINYL ESTRADIOL; LEVONORGESTREL	TABLET; ORAL- 0.03MG;0.15MG 28	LEVORA 0.15/30- 28	WATSON LABS
N203159		Yes	LEVONORGESTREL	INTRAUTERINE 13.5MG DEVICE; INTRAUTERINE	SKYLA	BAYER HLTHCARE
N021225		Yes	LEVONORGESTREL	INTRAUTERINE 52MG DEVICE; INTRAUTERINE	MIRENA	BAYER HLTHCARE
N021998	AB	Yes	LEVONORGESTREL	TABLET; ORAL 1.5MG	PLAN B ONE-STEP	DURAMED

A091328	AB	No	LEVONORGESTREL TABLET; ORAL 0.75MG	LEVONORGESTREL LUPIN LTD
A202508	AB	No	LEVONORGESTREL TABLET; ORAL 1.5MG	LEVONORGESTREL NOVEL LABS INC
A090740	AB	No	LEVONORGESTREL TABLET; ORAL 0.75MG	LEVONORGESTREL PERRIGO R AND D
N021045	AB	Yes	LEVONORGESTREL TABLET; ORAL 0.75MG	PLAN B TEVA BRANDED PHARM
A078666	AB	No	LEVONORGESTREL TABLET; ORAL 0.75MG	LEVONORGESTREL WATSON LABS
A078665	AB	Yes	LEVONORGESTREL TABLET; ORAL 0.75MG	LEVONORGESTREL WATSON LABS
A200670	AB	No	LEVONORGESTREL TABLET; ORAL 1.5MG	LEVONORGESTREL WATSON LABS INC

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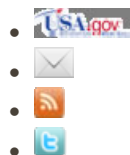
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Links on this page:



U.S. Food & Drug Administration

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations



Active Ingredient Search Results from "OB_OTC" table for query on "levonorgestrel."

Appl No	RLD ⁴ Active Ingredient	Dosage Form; Strength Route	Proprietary Name	Applicant
N021998	Yes LEVONORGESTREL	TABLET; ORAL 1.5MG	PLAN B ONE-STEP	DURAMED
A091328	No LEVONORGESTREL	TABLET; ORAL 0.75MG	LEVONORGESTREL	LUPIN LTD
A202508	No LEVONORGESTREL	TABLET; ORAL 1.5MG	LEVONORGESTREL	NOVEL LABS INC
A090740	No LEVONORGESTREL	TABLET; ORAL 0.75MG	LEVONORGESTREL	PERRIGO R AND D
N021045	Yes LEVONORGESTREL	TABLET; ORAL 0.75MG	PLAN B	TEVA BRANDED PHARM
A078665	Yes LEVONORGESTREL	TABLET; ORAL 0.75MG	LEVONORGESTREL	WATSON LABS
A200670	No LEVONORGESTREL	TABLET; ORAL 1.5MG	LEVONORGESTREL	WATSON LABS INC

[Return to Electronic Orange Book Home Page](#) ⁵

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through February, 2013

Patent and Generic Drug Product Data Last Updated: April 01, 2013


Links on this page:

1. <http://www.addthis.com/bookmark.php?u508=true&v=152&username=fdomain>
2. <http://www.addthis.com/bookmark.php>
3. <http://www.fda.gov/default.htm>
4. [http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#Reference Listed Drug](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#ReferenceListedDrug)
5. [../default.cfm](#)

Note: If you need help accessing information in different file formats, see [Instructions for Downloading Viewers and Players](#).

- [Accessibility](#)
- [Contact FDA](#)
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- [No Fear Act](#)
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- [Transparency](#)
- [Website Policies](#)

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)
[Email FDA](#)

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Links on this page:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

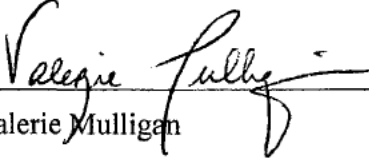
DORIS J BATES
04/30/2013

SHAW T CHEN
04/30/2013

1.3. Administrative Information

3. DEBARMENT CERTIFICATION

Teva Women's Health, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Valerie Mulligan
Senior Director, Regulatory Affairs

Feb 3, 2011
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 021998	NDA Supplement # S-002	If NDA, Efficacy Supplement Type: SE6
Proprietary Name: Plan B One-Step Established/Proper Name: Levonorgestrel Dosage Form: Tablet, 1.5 mg		Applicant: Teva Branded Pharmaceutical Products R&D, Inc. Agent for Applicant (if applicable): NA
RPM: Bates		Division: HFD-560, DNCE
<u>NDAs and NDA Efficacy Supplements:</u>	<u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u>	
Efficacy Supplement: 505(b)(1)	Not applicable.	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>September 9, 2012</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		CR issued on Dec. 7, 2011.
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain		
<i>Not applicable</i>		
❖ Application Characteristics²		
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):		
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan drug designation	<input type="checkbox"/> Rx-to-OTC full switch <input checked="" type="checkbox"/> Rx-to-OTC partial switch (extend lower OTC age limit from 17 to 15 years of age) <input type="checkbox"/> Direct-to-OTC	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies	REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required
Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request		
Comments: <i>No REMS, no accelerated approval provisions.</i>		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other -- TBD by OEP, Press office

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) Not applicable</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) Not applicable</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) Not applicable</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.) Not applicable</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: <i>Not applicable</i> Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner’s receipt of the applicant’s notice of certification?

Yes No

(Note: The date that the patent owner received the applicant’s notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If “Yes,” skip to question (4) below. If “No,” continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant’s notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If “No,” continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If “No,” the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If “No,” continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee

Yes No

NOT APPLICABLE

<p>bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner’s receipt of the applicant’s notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If “No,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If “Yes,” a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	✓
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	Included
Documentation of consent/non-consent by officers/employees	Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	CR Letter, December 7, 2011 AP Letter
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	OTC, N/A
• Original applicant-proposed labeling	OTC, N/A
• Example of class labeling, if applicable	OTC, N/A
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	None <i>OTC, N/A</i>
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	

³ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> • Most-recent draft labeling 	OTC labeling attached to AP letter
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	Proprietary Name approved at time of NDA approval. No name change associated with S-002.
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	OTC: DNRD Labeling Reviews 09/29/2011 10/27/2011 11/16/2011 09/06/2012 04/09/2013 4/30/2013
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	RPM filing review: 5/25/11 Not a (b)(2) Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	No
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: See Right. • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	Not applicable. Partial OTC switch covers only age groups for which the drug was previously approved as Rx-only. PREA is not triggered.
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Outgoing communications (<i>letters, emails, faxes, telecons</i>) 	See Tab
<ul style="list-style-type: none"> ❖ Internal memoranda, telecons, etc. 	None
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> • Regulatory Briefing (<i>indicate date of mtg</i>) 	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) check for meetings in IND file 	

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	
<ul style="list-style-type: none"> Other meetings 	Type B Meetings: May 22, 2007 June 1, 2009 April 28, 2010
❖ Advisory Committee Meeting(s)	No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
<ul style="list-style-type: none"> 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	09/05/2012
Division Director Summary Review (<i>indicate date for each review</i>)	11/30/2011 04/30/2013
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	10/25/2011 05/20/2012 04/05/2013
PMR/PMC Development Templates (<i>indicate total number</i>)	NONE
Clinical Information⁵	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	10/25/2011 05/20/2012 04/05/2013
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	10/25/2011 05/20/2012 04/05/2013
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	07/25/2011
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	In clinical review 10/05/2011
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	PMHS Review 10/11/2011
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	Not applicable
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	Not applicable - OTC
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	09/23/2011

⁵ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology		<i>None</i>	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>		None	
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>		None	
Biostatistics			
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>		N/A	
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>		10/12/2011 (concurrency)	
Statistical Review(s) <i>(indicate date for each review)</i>		10/12/2011	
Clinical Pharmacology		<i>None</i>	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>		NONE	
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>			
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>			
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>			
Nonclinical		<i>None</i>	
❖ Pharmacology/Toxicology Discipline Reviews		NONE	
<ul style="list-style-type: none"> • ADP/T Review(s) <i>(indicate date for each review)</i> • Supervisory Review(s) <i>(indicate date for each review)</i> • Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i> 			
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>			
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>			
❖ ECAC/CAC report/memo of meeting			
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>			
Product Quality			<i>None</i>
❖ Product Quality Discipline Reviews			NONE
<ul style="list-style-type: none"> • ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i> • Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i> • Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i> 			
❖ Microbiology Reviews			
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		NOT NEEDED	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		None	

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	N/A
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	N/A
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	N/A
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Not applicable
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	Not applicable

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

DORIS J BATES
04/30/2013

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT


With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	Please see attached list	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Valerie Mulligan	TITLE Senior Director, Regulatory Affairs
FIRM/ORGANIZATION Teva Women's Health, Inc.	
SIGNATURE 	DATE (mm/dd/yyyy) 02/01/2011

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right.

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850

Plan B One Step (levonorgestrel) tablet 1.5 mg
NDA 21-998

Teva Women's Health, Inc.

1.3. Administrative Information

4. FINANCIAL CERTIFICATION AND DISCLOSURE

Table 1: List of Investigators for Clinical Study DR-LEV-302

Site Number Name Address	Principal Investigator Sub-investigators	Financial Disclosure Information Obtained (yes/no)*	Disclosable Information (yes/no)**
001 UCSF San Francisco General Hospital 625 Petrero Avenue San Francisco, CA 94110	Raine-Bennett, Tina (b) (6)	Yes Yes Yes Yes Yes Yes	No No No No No No
002 Emory University School of Medicine 49 Jesse Hill Jr. Drive SE Atlanta, GA 30303	Cwiak, Carrie (b) (6)	Yes Yes Yes Yes Yes Yes	No No No No No No
003 Children's Hospitals and Clinics of Minnesota Teen Age Medical Service / TAMS 2425 Chicago Ave South Minneapolis, MN 55404	Aughey, David (b) (6)	Yes Yes Yes Yes Yes Yes Yes	No No No No No No No

Plan B One Step (levonorgestrel) tablet 1.5 mg
NDA 21-998

Teva Women's Health, Inc.

1.3. Administrative Information

<p>004 Hospital of the University of Pennsylvania 3701 Market Street Suite 810 Philadelphia, PA 19104</p>	<p>Schreiber, Courtney (b) (6)</p>	<p>Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes</p>	<p>No No No No No No No No No No</p>
<p>005 Children's Hospital Pittsburgh Oakland Medical Bldg. 3420 Fifth Avenue, Lower Level Pittsburgh, PA 15213</p>	<p>Sucato, Gina (b) (6)</p>	<p>Yes Yes Yes Yes</p>	<p>No No No No</p>



NDA 021998/S-002

INFORMATION REQUEST

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: Amy Hummel, M.S.
Associate Director, Regulatory Affairs
41 Moores Road, P.O. Box 4011
Frazer, PA 19355

Dear Ms. Hummel:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B One-Step® (levonorgestrel) tablet, 1.5 mg.

We also refer to your submissions dated March 13, 2013 and April 4, 2013.

We have the following requests for modification of your proposed labeling:

Changes Requested to Carton:

“Drug Facts” DIRECTIONS Section:

Revise the bullets in this section to read as follows:

- **women 15 years of age and older: take as soon as possible within 72 hours (3 days) after unprotected sex. The sooner you take it the better it will work.**
- **women under 15 years of age: talk to a doctor about emergency contraception options.**
- **if you vomit within 2 hours after taking the medication, call a healthcare professional to find out if you should repeat the dose.**

Principal Display Panel:

Remove the text in the upper left corner of the PDP that reads, (b) (4)
[REDACTED] Replace this text with a copy of the pink box that is currently positioned next to the “Drug Facts” box.

In addition, retain the pink box also in its current position next to the “Drug Facts” box.

Changes Requested to Clamshell Card Insert:

Remove the text on the front side of the clamshell that reads “New!”

We request a prompt written response in order to continue our evaluation of your supplemental application.

If you have questions, call Doris J. Bates, Ph.D., Regulatory Project Manager, at (301)796-1040.

Sincerely,

{See appended electronic signature page}

Dan Brum, Pharm.D., M.B.A., B.C.P.S., R.A.C
Acting Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

DORIS J BATES

04/09/2013

Signed on behalf of Dan Brum, Acting CPMS, Division of Nonprescription Clinical Evaluation.

DSI CONSULT: Request for Clinical Inspections

Date: 04/04/11

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Christina Chang, M.D., M.P.H., Medical Officer, DNCE
Lesley Furlong, M.D., M.S., Medical Team Leader, DNCE

From: Melissa Hancock Furness, CPMS, DNCE

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 21-998/S-002
Applicant/ Applicant contact information (to include phone/email): Teva
Drug Proprietary Name: Plan B On-Step (levonorgestrel) tablets
NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): Yes
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): This supplement does not add a new indication. This supplement seeks to expand the existing OTC consumer population for this drug product.

PDUFA:
Action Goal Date: 12/07/11
Inspection Summary Goal Date: 10/07/11

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
University of California, San Francisco General Hospital 6D1001 Petrero San Francisco, CA 94110	DR-LEV-302	316	See Information Under Section I (General) of this consult form.

III. Site Selection/Rationale

Rationale for DSI Audits

This is a pivotal study conducted to support the OTC availability of this drug product in the proposed expanded age group. The UCSF site enrolled more than 92% of study subjects. The sponsor did not conduct an internal audit for this study.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

IV. Tables of Specific Data to be Verified (if applicable)

Not applicable.

Should you require any additional information, please contact Melissa Furness at 301-796-0893 or Christina Chang at 301-796-2078.

Concurrence: (as needed)

_____ *LF* _____ Medical Team Leader
_____ *CC* _____ Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

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/s/

MELISSA H FURNESS
04/04/2011



NDA 021998/S-002

INFORMATION REQUEST

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: Amy Hummel, M.S.
Associate Director, Regulatory Affairs
41 Moores Road, P.O. Box 4011
Frazer, PA 19355

Dear Ms. Hummel:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B One-Step® (levonorgestrel) tablet, 1.5 mg.

We also refer to your submission dated March 13, 2013.

We note that your submission dated March 13, 2013 contains no labeling. Please confirm that:

1. There are no changes to the following labeling:
 - a. immediate container label (1-count blister) submitted October 21, 2011
 - b. outer carton (retail/trade) label submitted March 09, 2012
 - c. outer carton (clinic) label submitted March 09, 2012
 - d. packaging tray label submitted November 04, 2011
 - e. consumer information leaflet submitted December 07, 2011
2. There is no additional labeling associated with the proposed clamshell.

We request a prompt written response in order to continue our evaluation of your supplemental application.

If you have questions, call Doris J. Bates, Ph.D., Regulatory Project Manager, at (301)796-1040.

Sincerely,

{See appended electronic signature page}

Dan Brum, Pharm.D., M.B.A., B.C.P.S., R.A.C
Acting Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

DANIEL BRUM
03/27/2013



NDA 021998/S-002

**ACKNOWLEDGEMENT –
CLASS 2 RESPONSE**

Teva Women's Health, Inc.
Attention: Valerie M. Mulligan
Senior Director, Regulatory Affairs
425 Privet Road
P.O. Box 1005
Horsham, PA 19044

Dear Ms. Mulligan:

We acknowledge receipt of your March 9, 2012 resubmission to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B® One-Step (levonorgestrel) tablets, 1.5 mg.

We acknowledge your request to be classified as a class 1 resubmission. However, because your submission includes a new proposed paradigm, i.e., the restricted over-the-counter marketing of this drug product to women 15 years of age and older, we consider it to be a significant change from your original proposal which involved no restrictions on the nonprescription sales of this drug product to all women of child bearing potential. Thus, we consider this a complete, class 2 response to our December 7, 2011, action letter, and the user fee goal date is September 9, 2012.

If you have any questions, call me at (301) 796-0893.

Sincerely,

{See appended electronic signature page}

Melissa Hancock Furness
Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

MELISSA H FURNESS
03/23/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Tina Raine-Bennett, M.D.
New Generation Health Center
625 Potrero Avenue
San Francisco, CA 94110

Dear Dr. Raine-Bennett:

The purpose of this letter is to inform you of the findings of a Food and Drug Administration (FDA) inspection conducted at your site. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of human subjects of those studies have been protected. Between July 6, 2011 and July 12, 2011, Ms. Marie K. Kinkade representing the FDA, met with you and your site staff to review your conduct of a clinical investigation (Protocol Plan B One Step[®] Dr-Lev-302, entitled "Plan B[®] 1.5 Emergency Contraception Actual Use Study in Adolescents"), of the investigational drug levonorgestrel 1.5 (Plan B[®] 1.5) for Teva Women's Health Research.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Kinkade during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Susan D. Thompson, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Office of Scientific Investigations
Bldg. 51, Rm. 5350
Office of Compliance
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

SUSAN D THOMPSON
11/04/2011



NDA 021998/S-002

LABELING COMMENTS

Teva Women's Health, Inc.
Attention: Valerie M. Mulligan
Senior Director, Regulatory Affairs
425 Privet Road
P.O. Box 1005
Horsham, PA 19044

Dear Ms. Mulligan:

Please refer to your February 7, 2011 Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B[®] One-Step (levonorgestrel) tablets, 1.5 mg.

We also refer to our April 22, 2011, letter in which we notified you of our target date of November 16, 2011 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

On October 21, 2011, we received your October 21, 2011 submission to this application that contained your proposed drug product labeling. Please find our proposed revisions that are listed below:

- Remove the claim [REDACTED] (b) (4) on all pieces of your proposed drug product labeling.

In general, we do not think that physician recommended promotional labeling claims are appropriate for nonprescription products. [REDACTED] (b) (4)

If you have any questions, call Melissa Hancock Furness, Supervisory Regulatory Project Manager, at (301) 796-0893.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, M.D., M.S.
Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

ANDREA LEONARD SEGAL
11/01/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation

E-MAIL TRANSMITTAL SHEET

DATE: June 16, 2010

To: Valerie Mulligan Sr. Director, Regulatory Affairs	From: Melissa Hancock Furness Chief, Project Management Staff
Company: Teva Women's Health	Division of Nonprescription Clinical Evaluation
E-mail: valerie.mulligan@tevausa.com	E-mail: melissa.furness@fda.hhs.gov
Phone number: 215-293-7228	Phone number: 301-796-0893

Subject NDA 21-998/S-002 – Plan B One-Step labeling comments
:

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-0893. Thank you.

The following comments are in response to your February 7 and March 31, 2011 submissions that contained proposed labeling revisions for NDA 21-998/S-002 – Plan B One-Step.

A. Carton Label Outside Drug Facts (Trade and Clinic Cartons)

1. The statement [REDACTED] (b)(4) is not acceptable. We consider this to be an inappropriate claim for an OTC product. Please remove this statement from the PDP.
2. We recommend that the strength be listed after the active ingredient name on the PDP to be consistent with other OTC drugs (i.e., “levonorgestrel 1.5 mg”).
3. The phrase [REDACTED] (b)(4) conveys a key safety message and should be retained on the PDP.
4. The word [REDACTED] (b)(4) is not acceptable in the labeling; [REDACTED] (b)(4)
5. The phrase [REDACTED] (b)(4) is unclear and does not add anything to the approved labeling. We recommend that you use the originally approved language: “One Tablet One Dose” instead of [REDACTED] (b)(4)

B. Carton Drug Facts Label (Trade and Clinic Cartons)

6. Moving the [REDACTED] (b)(4) is not acceptable. [REDACTED] (b)(4)
7. Moving the [REDACTED] (b)(4) is not acceptable. [REDACTED] (b)(4)
8. A statement indicating that the product is “for women only” needs to be included on the carton or the Drug Facts section of the label. We recommend adding this information as the first bullet under the *Directions* section of Drug Facts.
9. Under the *Other information* heading, [REDACTED] (b)(4) is not acceptable. [REDACTED] (b)(4)
The original language should be retained.
10. Remove the period from the end of bulleted statements comprised of only one statement (first and fifth bullets under *Other information*).

C. Consumer Information Leaflet

11. The statement [REDACTED] (b) (4) is not acceptable. We consider this to be an inappropriate claim for an OTC product. Please remove this statement from Consumer Information Leaflet as well.
12. The word [REDACTED] (b) (4) is not acceptable. [REDACTED] (b) (4) See comment #4 above.
13. The claim [REDACTED] (b) (4) is not acceptable. Replace the first sentence under the subheading “What Plan B One-Step is not” with the previously approved statement: “Plan B One-Step will not work if you are already pregnant and will not affect an existing pregnancy.”
14. The proposed revision under the subheading “How does Plan B One-Step work?” is not acceptable. The original language should be used; however, changing “over 35 years” to “several decades” is acceptable. Change the word [REDACTED] (b) (4) to “tablet” under this heading when referring to Plan B One-Step.
15. The proposed revision under the subheading “How can I get the best results from Plan B One-Step?” is not acceptable. With the exception of changing “a few days” to “72 hours (3 days)” for precision, this section should not be revised. The statement [REDACTED] (b) (4)
16. Under the subheading “How will I know [REDACTED] (b) (4) Plan B One-Step worked?”, remove the word [REDACTED] (b) (4) from the subheading and revise the first sentence to read as follows: “You will know Plan B One-Step worked when you get your next period, which should come at the expected time, or within a week of the expected time.”
17. Under the subheading “Will I experience any side effects?”, we recommend bulleted statements to improve clarity and to highlight important information. Move the statement about a missed period to be the first statement since it is important information. Modify this section to read as follows:
 - “• some women may have changes in their period, such as a period that is heavier or lighter or a period that is early or late. **If your period is more than a week late, you maybe pregnant.**
 - if you have severe abdominal pain, you may have an ectopic pregnancy, and should get immediate medical attention.
 - when used as directed, Plan B One-Step is safe and effective. Side effects include changes in your period, nausea, lower stomach (abdominal) pain, tiredness, headache, dizziness, and breast tenderness.
 - if you vomit within 2 hours of taking the medication, call a healthcare professional to find out if you should repeat the dose.”

D. Immediate Container Label

18. The immediate container (blister card) label was not submitted for review. Please submit the immediate container (blister card) label.

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/s/

MELISSA H FURNESS
09/30/2011

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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			Pediatric and Maternal Health Staff Request for Consultation	
TO: CDER Pediatric and Maternal Health Staff (<i>please check</i>) Attention: Lisa Mathis, M.D., Director PMHS			FROM (Lesley-Anne Furlong, M.D., M.S., DNCE Clinical Team Leader	
Pediatrics x Maternal Health <input type="checkbox"/> Both <input type="checkbox"/>				
DATE 30-Jul-2011	IND NO.	NDA/BLA NO. 21998/S-002	TYPE OF DOCUMENT Efficacy supplement	DATE OF DOCUMENT 7-Feb-2011
NAME OF DRUG Levonorgestrel tablet 1.5 mg/Plan B One-Step		NAME OF FIRM Teva	CLASSIFICATION OF DRUG progestin	PDUFA Goal Date 7-Dec-2011
Requested Consult Completion Date: 22-Sep-2011		<input type="checkbox"/> Urgent* (< 14 days)	<input type="checkbox"/> Priority (14-29 days)	xRoutine \geq 30 days
*Note: Any consult requests with a desired completion date of < 14 days from receipt must receive prior approval from PMHS team leaders. Also, please check one of the three boxes above and also put in a due date.				
REASON FOR REQUEST				
Pediatrics:			Maternal Health Team:	
<input type="checkbox"/> Labeling Review <input type="checkbox"/> Written Request/PPSR <input type="checkbox"/> PREA PMR/General Regulatory Question <input type="checkbox"/> SPA <input type="checkbox"/> Action Letter Review <input type="checkbox"/> 30-day IND Review <input type="checkbox"/> Other Protocol Review <input type="checkbox"/> Meeting Attendance <input type="checkbox"/> PeRC Preparation Assistance <input checked="" type="checkbox"/> Other (please explain): suggested by upper management staff (Jane Axelrad and Sandra Kweder) at NDA mid-cycle meeting			<input type="checkbox"/> Labeling Review <input type="checkbox"/> Pregnancy Exposure Registry (protocol or report) <input type="checkbox"/> Clinical Lactation Study (protocol or report) <input type="checkbox"/> Pregnancy PK (protocol or report) <input type="checkbox"/> 30-day IND Review <input type="checkbox"/> Risk Management – Pregnancy Prevention and Planning <input type="checkbox"/> Evaluation of possible safety signal <input type="checkbox"/> Guidance development <input type="checkbox"/> Other (please explain):	
Link to electronic submission (if available): http://darts.fda.gov:9602/darts/viewEDR.do?suppDocId=7371554			Materials to be reviewed: Dr. Galson's memos, applicant's Clinical Overview (module 2.5) of submission(Please see relevant attachments)	
<p>1. Please briefly describe the submission including drug's indication(s): Reduces chance of pregnancy after unprotected sex</p> <p>2. Describe in detail the reason for your consult. Include specific questions: The applicant seeks to change the marketing status of Plan B One-Step from prescription (Rx) to over-the-counter (OTC) for women who are younger than 17 years old. Plan B One-Step is currently approved OTC for women who are at least 17 years of age and by prescription for those ages 16 years and younger. To support nonprescription availability for those less than 17 years old, FDA directed the applicant to address Dr. Galson's issues as enumerated in his memos regarding the related product, Plan B, dated 6-May-2004 and 26-Aug-2005 (see attached). Dr. Galson involved the pediatric staff in preparing his opinions. A series of reviews, meetings, and agreements (in which DNCE, Dr. Galson, others from upper management, and pediatrics participated) resulted in the advice FDA provided to Teva and, thus, in the present submission.</p> <p>Consequently, to support the expansion of the OTC population, the applicant has provided a label comprehension study, an actual use study, a literature review, and a postmarketing safety update. The applicant does not propose any changes in the product, its indication, its dosing regimen, or the population for whom it is indicated. If this supplemental NDA is approved, women less than 17 will be able to access the product OTC. The DNCE's review is ongoing.</p> <p>Please look at the provided documents and provide comments if you deem necessary.</p> <p>3. Meeting dates: Team meeting #4 is on 23-Aug-2011 at 11 am</p>				

4. DARRTS Reference ID # for Prior Peds or Maternal Health consults for this product (within the last 3 years): DARRTS consult sent on 04/15/2010 (DARRTS supporting document number 56). Please see below.



PMHS Consult_Plan B
One-Step_04-15-10.i

5. Attachments:



clinical-overview.pdf Galson Plan B 2004 Plan B Galson memo
f (207 KB)... may memo.pdf... Aug 2005.pdf...

Review team:

Project Manager: Melissa Furness

Clinical reviewer & Team Leader: Christina Chang and Lesley Furlong

Pharmacology/Toxicology reviewer & Team Leader: not applicable

Clinical Pharmacology reviewer & Team Leader: not applicable

Other: Social Scientist: Murewa Oguntimein; Statistics: Rima Izem and Yan Wang

PRINTED NAME or SIGNATURE OF REQUESTOR:

Lesley Furlong

METHOD OF DELIVERY (Please check)

DARRTS EMAIL HAND
 OTHER

Version: DARRTS 06/01/2011

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/s/

MELISSA H FURNESS
07/22/2011

LESLEYANNE A FURLONG
07/22/2011



NDA 021998/S-002

FILING COMMUNICATION

Teva Women's Health, Inc.
Attention: Valerie M. Mulligan
Director, Regulatory Affairs
425 Privet Road
P.O. Box 1005
Horsham, PA 19044

Dear Ms. Mulligan:

Please refer to your Supplemental New Drug Application (sNDA) dated February 7, 2011, received February 7, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Plan B[®] One-Step (levonorgestrel) tablets, 1.5 mg.

We also refer to your submissions dated March 31, April 4, and April 6, 2011.

This supplemental application proposes to expand the existing nonprescription patient population to allow for the nonprescription availability of Plan B[®] One-Step for all women of child-bearing potential.

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is December 7, 2011.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 16, 2011.

During our filing review of your application, we identified the following potential review issues and request that you submit the following information:

1. Provide updated safety information for the 12 subjects who had used Plan B[®] One-Step but had not completed all three follow-up contacts by the release date of the DR-LEV-302 study report.
2. Supply Drug Abuse Warning Network (DAWN) and American Association of Poison Control Centers (AAPCC) data for levonorgestrel. If you do not supply these data, address why your supplement does not need to include DAWN and AAPCC data, and provide a justification as to why Plan B[®] One-Step is unlikely to have abuse potential.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the supplemental application.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Melissa Hancock Furness, Regulatory Project Manager, at (301) 796-0893.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, M.D., M.S.
Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

ANDREA LEONARD SEGAL
04/22/2011



NDA 021998/S-002

**ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT**

Teva Women's Health, Inc.
Attention: Valerie M. Mulligan
Senior Director, Regulatory Affairs
425 Privet Road
P.O. Box 1005
Horsham, PA 19044

Dear Ms. Mulligan:

We have received your February 7, 2011, Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 021998
SUPPLEMENT NUMBER: 002
PRODUCT NAME: Plan B[®] One-Step (levonorgestrel) tablets, 1.5 mg
DATE OF SUBMISSION: February 7, 2011
DATE OF RECEIPT: February 7, 2011

This supplemental application proposes to expand the existing nonprescription patient population to allow for the nonprescription availability of Plan B[®] One-Step for all women of child-bearing potential.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 8, 2011, in accordance with 21 CFR 314.101(a).

If the application is filed, the PDUFA goal date will be December 7, 2011.

We considered your request for a Priority review, and it has been determined that this application qualifies for a Standard 10-month review. This supplement does not qualify for a Priority Review under Section 505A of the Act because your supplement does not include data to fulfill or partially fulfill a pediatric written request that was issued to you by the Agency. Furthermore, this supplement does not qualify for a Priority Review as it has been determined by the review team that the proposed expansion of the nonprescription population does not provide "a safe and

effective therapy where no satisfactory alternative therapy exists” or “a significant improvement compared to marketed products.”

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, “Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank,” [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, “Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007,” that describes the Agency’s current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 021998/S-002** submitted on February 7, 2011, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call me at (301) 796-0893

Sincerely,

{See appended electronic signature page}

Melissa Hancock Furness
Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MELISSA H FURNESS
03/17/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-998

MEETING MINUTES

Duramed Pharmaceuticals, Inc.
Attention: Michele G. Walsh
Director, Clinical Regulatory Affairs
425 Privet Road
Horsham, PA 19044

Dear Ms. Walsh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B[®] One-Step (levonorgestrel) tablets, 1.5 mg.

We also refer to the meeting between representatives of your firm and the FDA on April 28, 2010. The purpose of the meeting was to discuss your planned Proposed Pediatric Study Request and the potential for full OTC availability of this product.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Melissa Furness, CPMS, at (301) 796-0893.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, M.D.
Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

NDA 21-998
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Date and Time: April 28, 2010, 3:30 – 4:30 P.M., EST
Meeting Location: White Oak CDER Office Building 22
Conference Room 1417
10903 New Hampshire Avenue
Silver Spring, MD 20993

Application Number: NDA 21-998

Product Name: Plan B[®] One-Step (levonorgestrel)

Type of Meeting: Type B

Meeting Chair: Andrea Leonard-Segal, M.D., Director

Meeting Recorder: Melissa Furness, Chief, Project Management Staff

FDA ATTENDEES:

Division of Nonprescription Clinical Evaluation

Andrea Leonard-Segal, M.D., Director
Joel Schiffenbauer, M.D., Deputy Director
Melissa Furness, Chief, Project Management Staff
Lesley Furlong, M.D., Medical Team Leader
Christina Chang, M.D., Medical Officer
CAPT Laura Shay, R.N., Ph.D., C-ANP, Social Science Analyst
Neel Patel, Pharm.D., Regulatory Project Manager

Division of Reproductive and Urologic Products

Lisa Soule, M.D., Medical Team Leader
Daniel Davis, M.D., Medical Officer

Office of Drug Evaluation IV

Charles Ganley, M.D., Director
Leah Christl, Ph.D., Associate Director for Regulatory Affairs

Office of New Drugs

John Jenkins, M.D., Director

Pediatric and Maternal Health Staff

Lisa Mathis, M.D., Director
Rosemary Addy, Project Management Team Leader
Hari Cheryl Sachs, M.D., Medical Team Leader

NDA 21-998
Meeting Minutes

Amy Taylor, M.D., Medical Officer

Office of Regulatory Policy

Jane Axelrad, J.D., Director

Office of Chief Counsel

Heidi Gertner, J.D., Associate Chief Counsel

Karen Schifter, J.D., Associate Chief Counsel

Kim Dettelbach, J.D., Associate Chief Counsel

SPONSOR ATTENDEES:

Amy Niemann, General Manager, Teva Women's Health, Inc.

Kathy Reape, MD, FACOG Vice President, Women's Health Research, Teva Branded
Pharmaceutical Products R&D, Inc.

Nancy Ricciotti, MSN, Senior Director, Clinical Research, Women's Health Research, Teva
Branded Pharmaceutical Products R&D, Inc.

Valerie Mulligan, Senior Director, Regulatory Affairs, Women's Health Research, Teva Branded
Pharmaceutical Products R&D, Inc.

Michele Walsh, Director, Regulatory Affairs, Women's Health Research, Teva Branded
Pharmaceutical Products R&D, Inc.

Amy Hummel, MS, Manager, Regulatory Affairs, Women's Health Research, Teva Branded
Pharmaceutical Products R&D, Inc.

Pat Jaworski, Senior Director, Regulatory Affairs, Teva Pharmaceuticals USA

(b) (4)

Tina Raine-Bennett, MD, MPH, consultant, UCSF

(b) (4)

1.0 BACKGROUND

Plan B[®] One-Step is currently approved as prescription product for women who are younger than 17 years of age and as an over-the-counter (OTC) product for women who are 17 years of age and older. Plan B[®] One-Step is given as a single dose for emergency contraception. Duramed Pharmaceuticals submitted a meeting request to the FDA for a type B meeting on December 17, 2009 to discuss their planned Proposed Pediatric Study Request and the potential for full OTC availability of Plan B[®] One-Step (levonorgestrel).

2.0 MEETING OBJECTIVES

The purpose of the meeting was to discuss Duramed's [Teva's] planned Proposed Pediatric Study Request and the potential for full OTC availability of Plan B[®] One-Step.

3.0 DISCUSSION

Preliminary responses to the questions enclosed in the March 10, 2010, meeting package were sent to Duramed Pharmaceuticals via e-mail on April 27, 2010. These questions and preliminary

FDA responses are listed below in italics. Duramed Pharmaceuticals had no questions regarding the FDA preliminary responses. Following introductions, the meeting agenda consisted of a Power Point presentation by Duramed Pharmaceuticals (see attached) and further discussion based on the preliminary responses from the FDA. A record of the discussion that occurred during the meeting is presented following the question and response to which the discussion pertained.

3.1 Question 1

Please comment on the use of DR-LEV-302 without quota enrollment in the 11-13 age group as a study for which FDA would issue a written request.

FDA Preliminary Response:

The FDA has previously communicated that Actual Use Study data in the pediatric population are necessary to support the OTC labeling of levonorgestrel for emergency contraception for that age group. We are open to issuing a written request to evaluate the safety and effectiveness of levonorgestrel in pediatric patients. We remind you that under the Best Pharmaceuticals for Children Act (BPCA) FDA written requests address data needs for the active moiety, not a specific drug product. You should submit a Proposed Pediatric Study Request (PPSR) for our consideration. If you choose to submit a PPSR solely for Plan B® One-Step, you should include a valid scientific rationale as to why the requested study should not also include Plan B®. For example, you would need to justify why the data generated from a Plan B® One-Step Actual Use Study could be extrapolated to Plan B®, particularly since the latter has a more complicated dosing regimen.

Based on the material submitted in your meeting package, it appears that you have provided adequate information to justify removing the quota for enrollment of 11 to 13-year-olds as currently specified in your actual use study protocol. If you wish to formalize this change, you should submit an amendment to your IND and include in that amendment your explanation for making the change. In the absence of an analyzable cohort of children ages 11 – 13 in the actual use study, it is important that you provide data from label comprehension study(ies) based on individual age versus grouping ages to allow for targeted analyses by age.

Any written request that we issue will include all the age groups specified in your original actual use study protocol, even if the written request does not include a specified minimum number of patients in each designated age group. In your PPSR you should clearly delineate and justify your proposals for what studies should be included in the Agency written request.

Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

For additional information, we refer you to the Guidance for Industry: Qualifying for Pediatric Exclusivity under Section 505A of the Federal Food, Drug, and Cosmetic Act, at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080558.pdf>

Additional Discussion for Question 1:

FDA inquired as to the timing of Duramed Pharmaceuticals' planned (PPSR) submission. Duramed indicated that they plan to submit the PPSR as soon as possible. FDA asked Duramed if they had noted that FDA's preliminary response requested that the PPSR include a proposal for the entire moiety. Duramed acknowledged that this had been noted.

3.2 Question 2

Assuming that a written request is issued by the agency and is accepted by Duramed, and that Duramed submits a supplement to NDA 21-998 to remove the age restriction on OTC use based on DR-LEV-302 and DR-LEV-301, does the Agency confirm that, as per Section 505A (i)(1) of the Food Drug and Cosmetic Act, this NDA supplement would be considered a priority supplement and be subject to the performance goals for such?

FDA Preliminary Response:

Sections 505A (i)(1)(A) and 505A (i)(1)(B) of the Act provide that any application or supplement to an application under section 505 proposing a labeling change as a result of any pediatric study conducted pursuant to this section shall be considered to be a priority application or supplement and shall be subject to the performance goals established by the Commissioner for priority drugs. Assuming that the Agency issues a written request and you accept the written request, your supplement, when submitted, will be accepted for priority review and be subject to the performance goals of a priority review.

Additional Discussion for Question 2:

FDA inquired as to the timing of Duramed Pharmaceuticals' planned supplement to the NDA to add a new nonprescription patient population. Duramed Pharmaceuticals indicated that this submission is planned for first quarter 2011.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

- Duramed Pharmaceuticals plans to submit their proposed pediatric study request (PPSR) as soon as possible. Duramed understands that the PPSR should include a proposal for the entire moiety.
- Duramed Pharmaceuticals plans to submit their NDA supplement to add a new nonprescription patient population in the first quarter of 2011.

6.0 ATTACHMENTS AND HANDOUTS

Please see the attached sponsor presentation of preliminary data from their ongoing actual use study (DR-LEV-302). During Duramed Pharmaceutical's presentation, FDA asked clarifying questions regarding the timing of the recently added additional study sites. Duramed acknowledged that such preliminary data would not be subject to Agency review until the complete study report is submitted in the NDA efficacy supplement.



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San Francisco

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Plan B[®] 1.5 Actual Use Study Duramed Research Inc (Teva) Protocol DR-LEV-302 Status Report



**Bixby Center
for Global
Reproductive
Health**

*Tina Raine-Bennett MD, MPH - Professor
Bixby Center for Global Reproductive Health
Dept of Obstetrics Gynecology and Reproductive Sciences
University of California, San Francisco*

April 2010



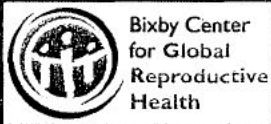
Research Team

- **Teva Pharmaceuticals**

- Nancy Riciotti, MSN
Senior Director, Clinical Research

- **UCSF**

- Tina Raine-Bennett, MD, MPH

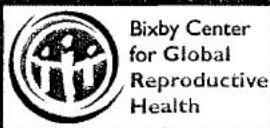


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Gynecology & Reproductive
Sciences
School of Medicine



Study Objectives

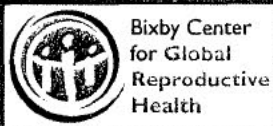
- **To determine under simulated OTC conditions whether females age 11-17 years can:**
 - appropriately self-select to use Plan B[®] 1.5
 - correctly use Plan B[®] 1.5
- **Status report study population:**
 - participants enrolled October 2008 through December 2009





Study Sites

- **San Francisco CA - October 2008**
 - New Generation Health Center, University of California San Francisco
- **Fremont CA - March 2009**
 - Tri-City Teen City Clinic, Tri-City Health Center
- **Daly City CA - September 2009**
 - Daly City Youth Health Center, San Mateo County Dept of Public Health
- **Atlanta GA - October 2009**
 - Grady Teen Services Program, Emory University School of Medicine at Grady Memorial Hospital
- **Philadelphia, PA - December 2009**
 - Penn Family Planning and Pregnancy Loss Center
- **Minneapolis MN - February 2010**
 - Teen Age Medical Service, Children's Hospitals and Clinics of Minnesota



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and Gynecology, University of California
San Francisco
www.ucsf.edu/ghr

2009 Unduplicated Clients Seen at Study Sites for Any Reason by Age

Age (yrs)	San Francisco CA	Fremont CA	Daly City CA	Atlanta GA
11	0	0	0	18
12	0	0	1	
13	4	2	29	
14	18	9	97	
15	79	86	126	
16	116	185	200	369
17	212	374	257	
Total	429	656	710	387



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Study Eligibility Criteria

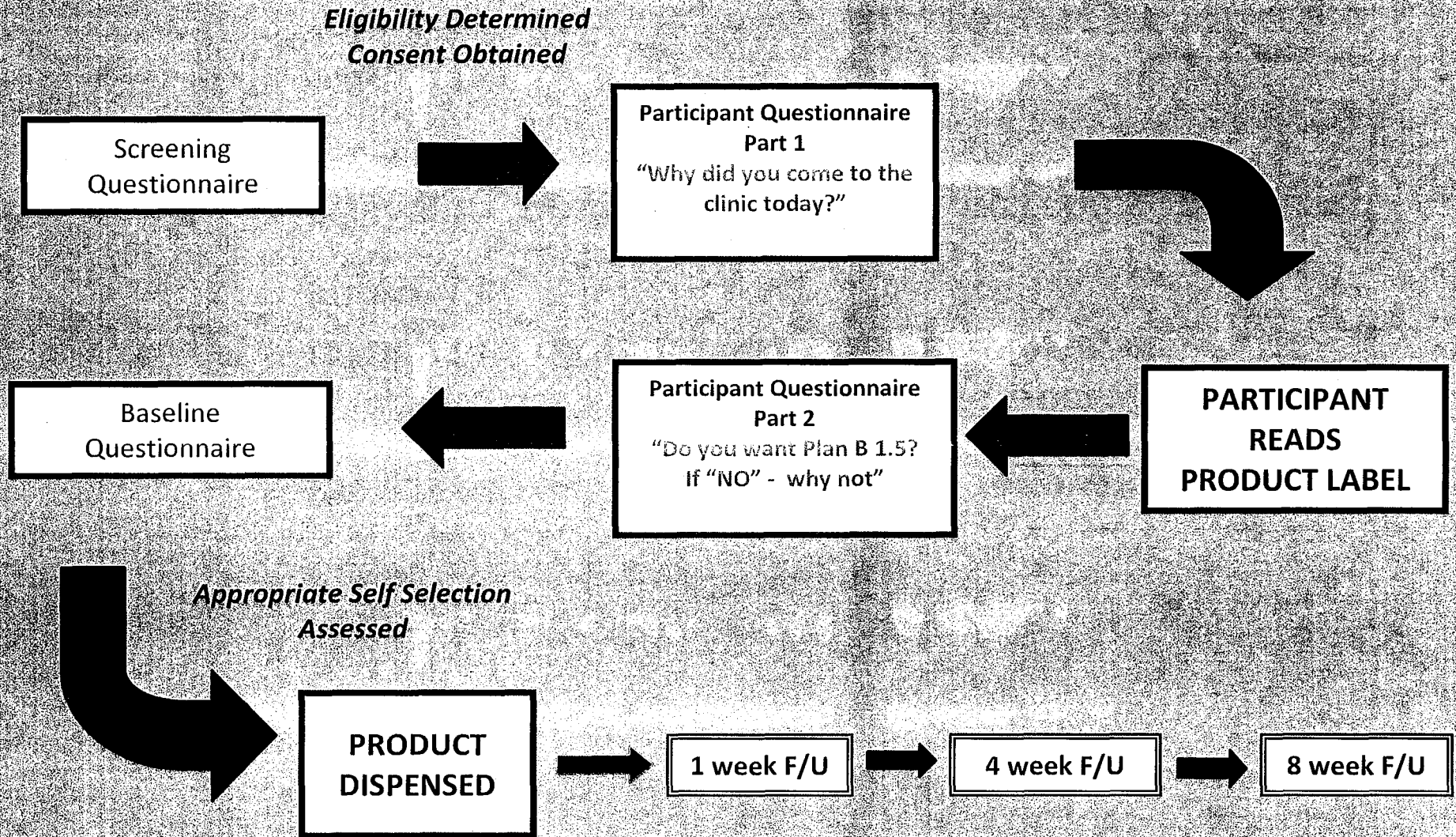
- **Age 11-17***
- **Reads and understands English**
- **Presented to clinic requesting ECP for own use**
- **Willing to use ECP after reading the label without talking to a clinic provider (Doctor, Nurse, or Counselor)**
- **Willing to complete study procedures and be contacted for follow-up**



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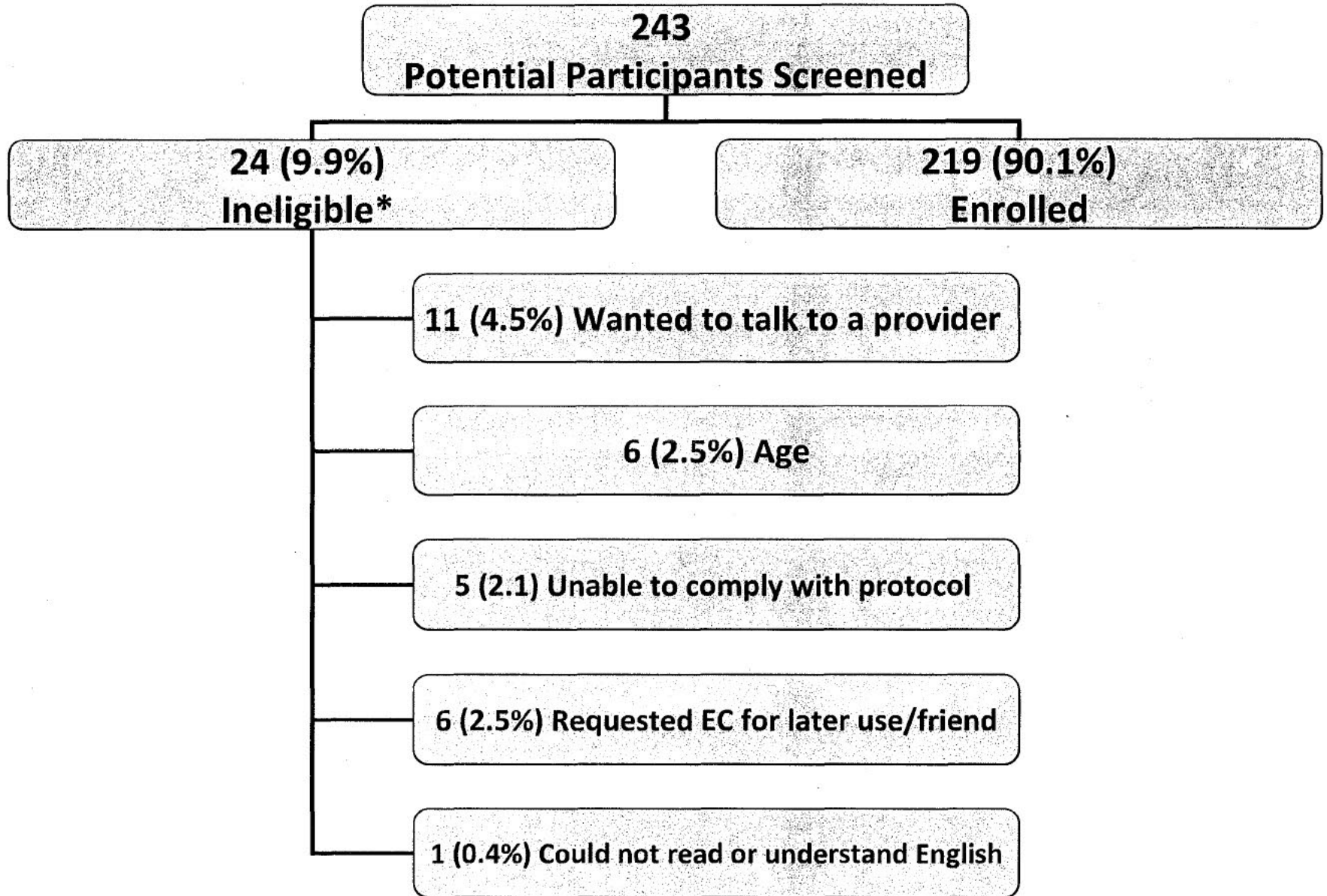
**Only San Francisco and Fremont sites enrolled 17 year old subjects*

Study Flow



(Chart Review of Study Period for EC Use at Clinic sites)

Study Screening and Enrollment



**More than one reason for ineligibility*

Baseline Study Demographics

Age by Site

Age (years)	San Francisco CA	Fremont CA	Daly City CA	Atlanta GA	Total N (%)
11	0	0	0	0	0 (0.0)
12	0	0	0	0	0 (0.0)
13	0	0	1	0	1 (0.5)
14	10	4	1	1	16 (7.3)
15	38	15	5	0	58 (26.5)
16	32	26	14	5	77 (35.2)
17	30	37	0	0	67 (30.6)
Total	110	82	21	6	219 (100)

Baseline Study Demographics

Race by Site

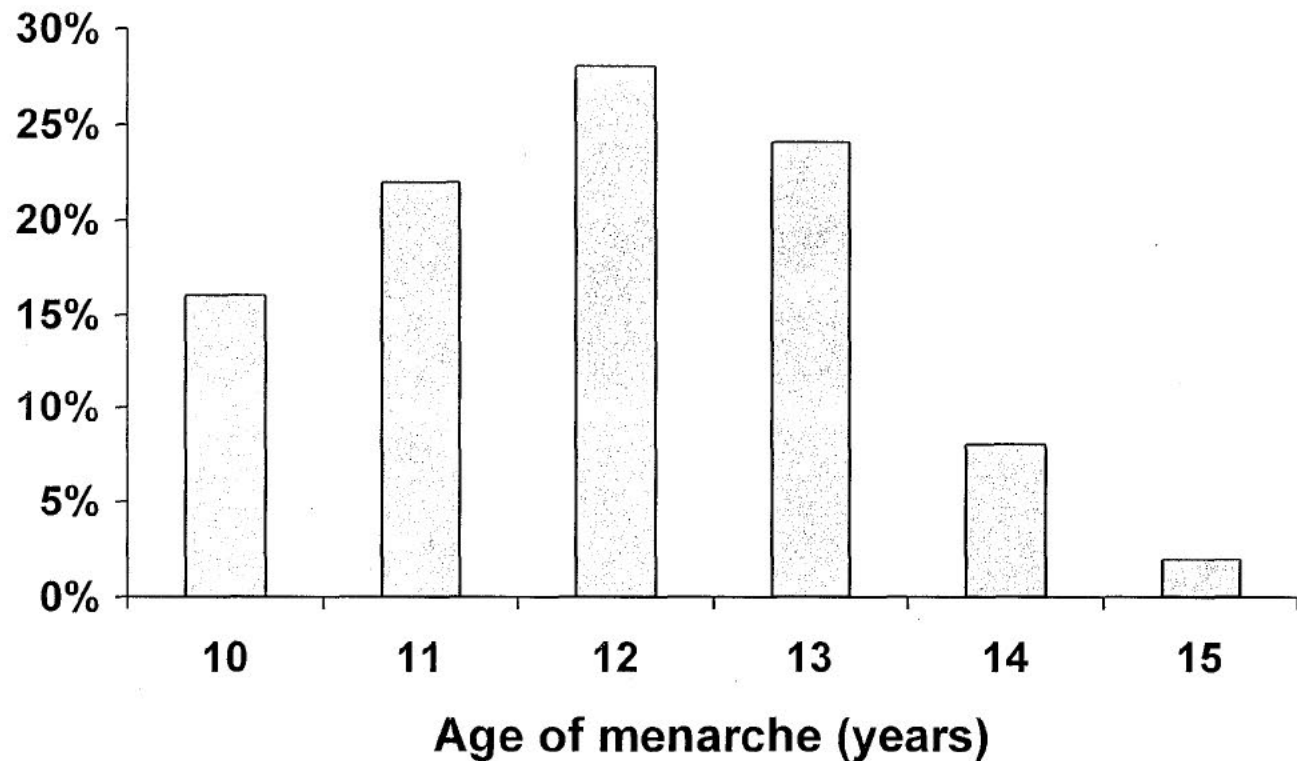
Race	San Francisco CA	Fremont CA	Daly City CA	Atlanta GA	Total N (%)
Latin American	72	29	7	0	108 (49.3)
African American	13	4	0	6	23 (10.5)
Multirace	7	7	3	0	17 (7.8)
White	2	25	1	0	28 (12.8)
Asian/PI	15	17	10	0	42 (19.2)
Native Amer/ Alaskan	1	0	0	0	1 (0.5)
Total	110	82	21	6	219 (100)



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Baseline Study Characteristics

Menarche (mean age= 11.9 years)



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Sciences

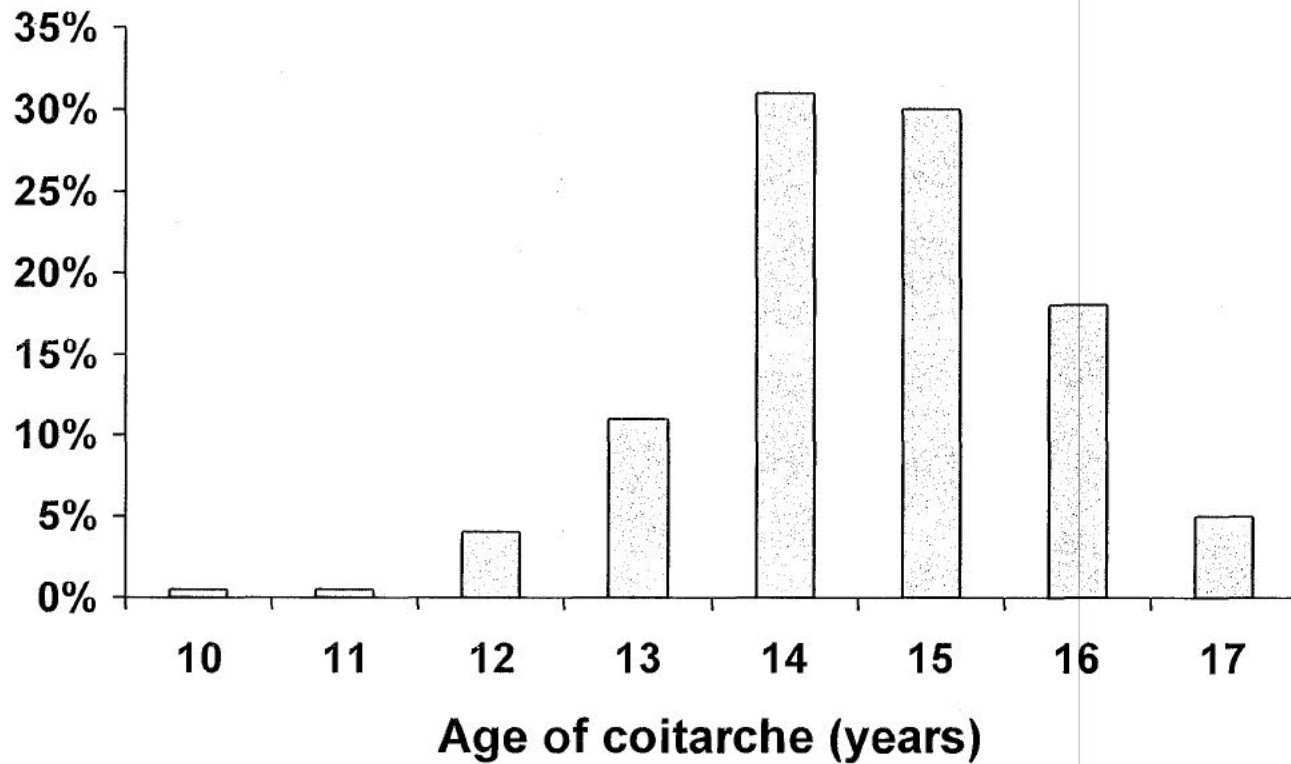
San Francisco, CA



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Baseline Study Characteristics

Coitarche (mean age = 14.6 yrs)



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Appropriate Self-Selection

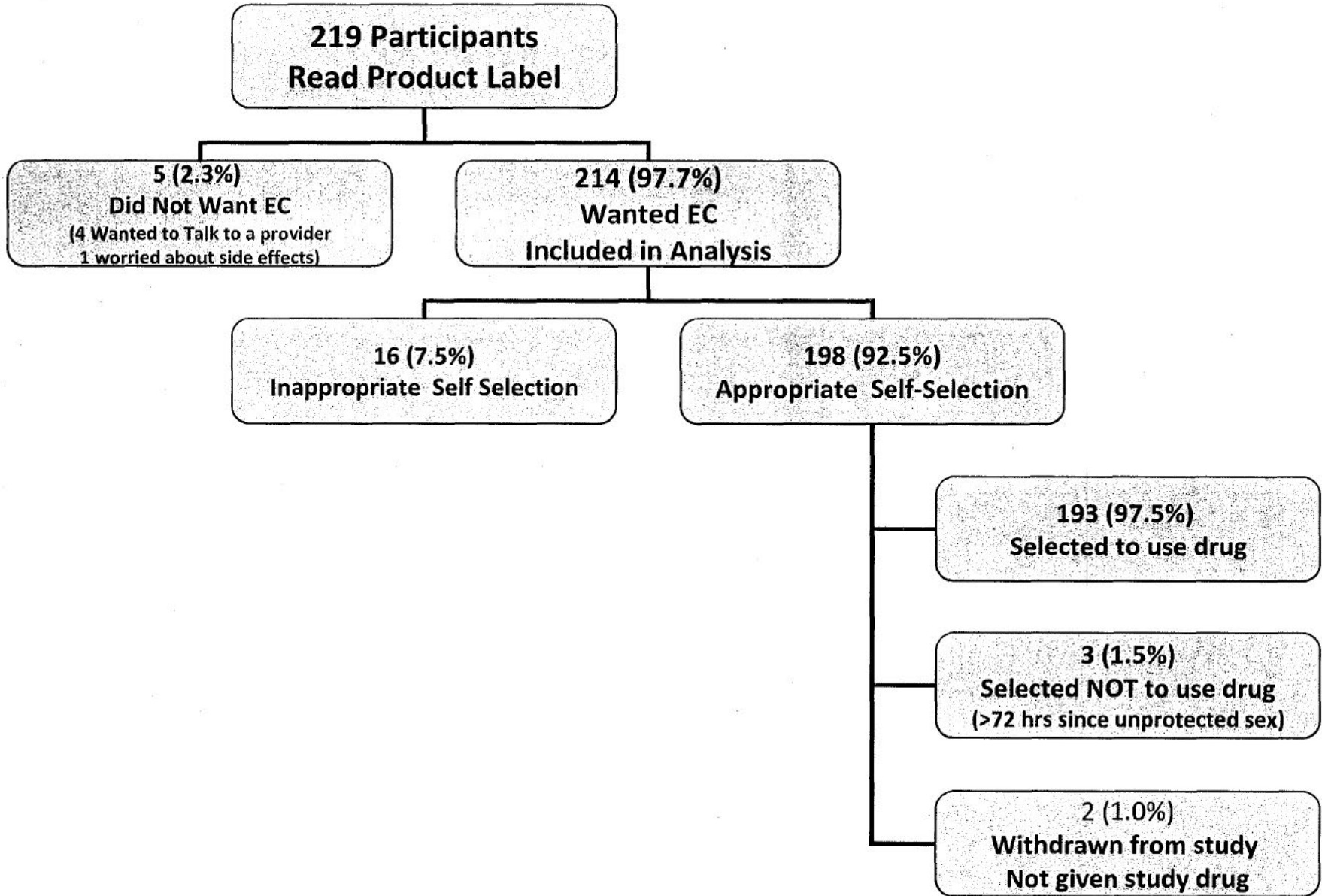
- **Selection for use of ECP as specified on the product label:**
 - Reason for which the product is indicated
 - Prevent pregnancy
 - Within 72 hours of unprotected sex
 - Not currently pregnant
 - Verbatim response on participant questionnaire
 - Pregnancy questions on baseline questionnaire
 - Not allergic to Levonorgestrel
 - Question on baseline questionnaire
- **Participants could also appropriately self-select NOT to use the product**



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Shobha Menon, MD

Appropriate Self-Selection



Self-Selection by Age*

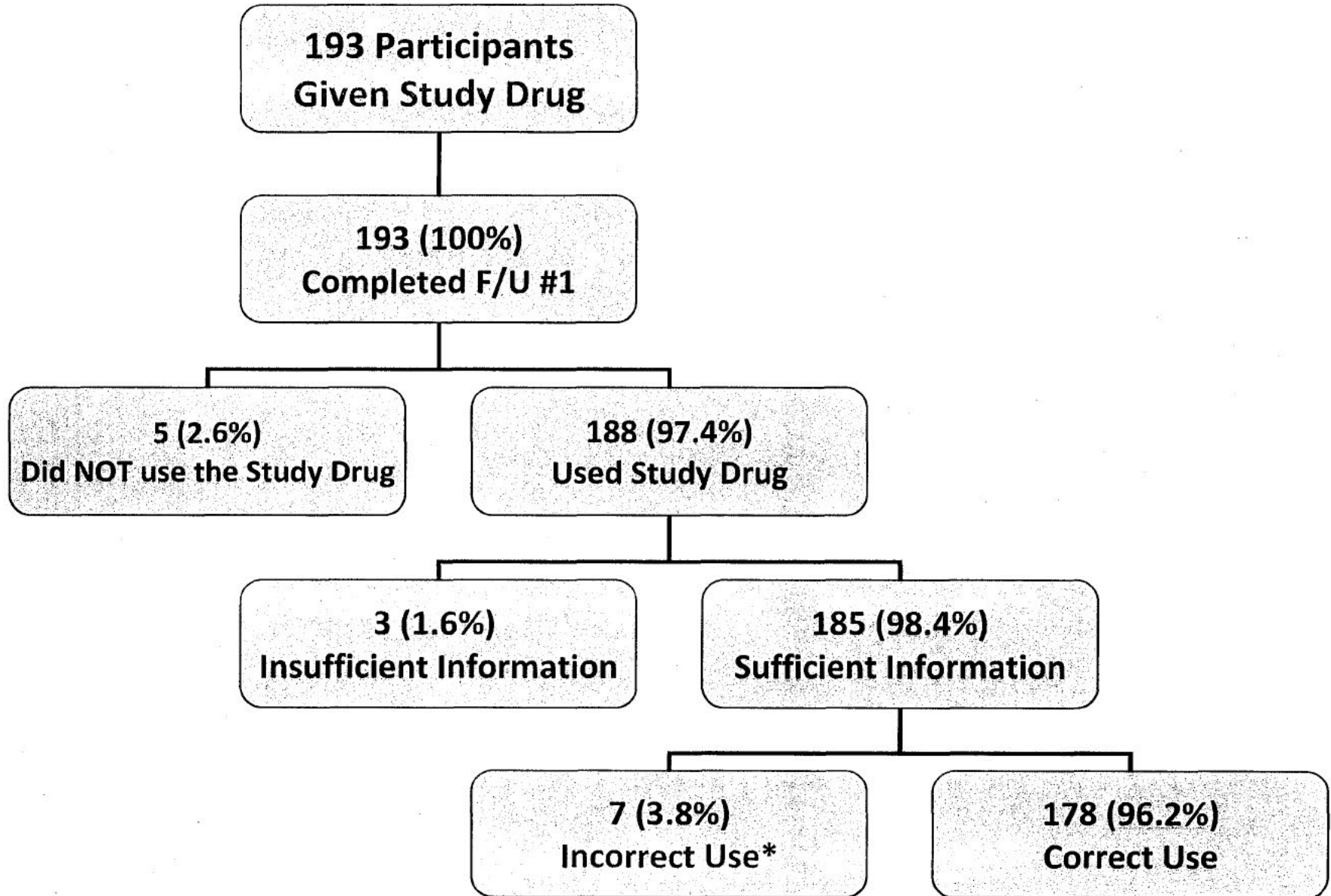
Age	Appropriate n (%)	Inappropriate n (%)	Total
13	0	1 (100%)	1
14	13 (81.3%)	3 (18.7%)	16
15	51 (91.1%)	5 (8.9%)	56
16	74 (98.7%)	1 (1.3%)	75
17	60 (90.9%)	6 (9.1%)	66
Total	198 (92.5%)	16 (7.5%)	214

**P=0.09 - Differences by age not statistically significant*

Correct Use

- **Participant took product according to the product label**
 - Taken for unprotected sex
 - As reported on Follow-up #1
 - Within 72 hours of unprotected sex
 - Time of drug use minus Time of unprotected sex reported on Follow-up #1
 - Not already pregnant
 - Report of pregnancy tests on Follow-up #1

Correct Use

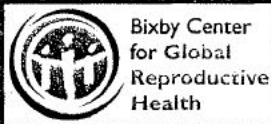


** All Incorrect use occurred 72 to 120 hrs after unprotected sex*



Summary

- **Limited number of participants less than age 15 due to small numbers of younger teens presenting for services**
- **92% of participants appropriately self-select to use (not use) the study drug**
- **96% correctly used the study drug**



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Sciences

San Francisco, California



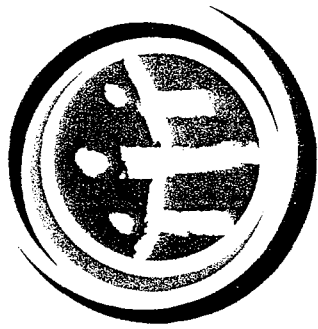
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Health**

Questions – Contact Dr. Tina Raine-Bennett
rainet@obgyn.ucsf.edu

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Backup Slides

UCSF

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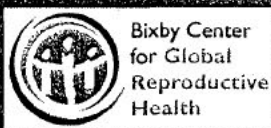
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Chart Review

24 Participants Did Not Receive the Study Drug 19 Chart review data available

- 3 of 4 participants who wanted to talk to a provider received EC from a provider
- 11 of 13 inappropriate self-selectors received EC from a provider
- 1 of 2 subjects who appropriately self-selected not to use the study drug received EC from a provider



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Gynecology & Reproductive
Sciences

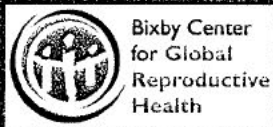
San Francisco, California



Baseline Study Characteristics

Prior ECP Use

- **102 (47%) Used ECP in the Past**
- **Source of ECP*:**
 - 87 (40.1%) Clinic
 - 27 (12.4%) Pharmacy
 - 28 (12.9%) Friend or Relative



Department of Obstetrics
Gynecology & Reproductive
Sciences

San Francisco, California

**Participants may have obtained EC from more than one source*

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-21998

GI-1

DURAMED
PHARMACEUTICA
LS INC

Plan B One-Step

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANDREA LEONARD SEGAL
05/25/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-045
NDA 21-998

Duramed Research, Inc.
Attention: Michele Walsh
Director, Clinical Regulatory Affairs
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004

Dear Ms. Walsh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B[®] (levonorgestrel, 0.75 mg) Tablets (NDA 21-045) and Plan B One-Step[®] (levonorgestrel, 1.5 mg) Tablets (NDA 21-998).

We also refer to the meeting between representatives of your firm and the FDA on June 1, 2009. The purpose of the meeting was to discuss a full OTC switch for both the Plan B[®] and Plan B One-Step[®] products.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Leah Christl, Associate Director for Regulatory Affairs, Office of Nonprescription Products, at 301-796-0869, or Pamela Lucarelli, Regulatory Health Project Manager, Division of Reproductive and Urologic Products, at (301) 796-3961.

Sincerely,
{See appended electronic signature page}

Andrea Leonard-Segal, M.D.
Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B

Meeting Category: Pre-Supplemental NDA

Meeting Date and Time: June 1, 2009
11:00 a.m. – 12:30 p.m. EST

Location: White Oak CDER Office Building 22
10903 New Hampshire Avenue
Conference Room 1313
Silver Spring, MD 20993

Applications: NDA 21-045 and NDA 21-998

Product Names: Plan B ® (levonorgestrel, 0.75 mg) tablets (NDA 21-045)
and Plan B One-Step ® (levonorgestrel, 1.5 mg) tablets
(NDA 21-998)

Sponsor Name: Duramed Research, Inc.

Meeting Requestor: Michele Walsh
Director, Clinical Regulatory Affairs

Meeting Chair: Andrea Leonard-Segal, M.D.
Director
Division of Nonprescription Clinical Evaluation

Meeting Recorder: Leah Christl, Ph.D.
Associate Director for Regulatory Affairs
Office of Nonprescription Products

Meeting Attendees:

FDA Attendees:

Office of Nonprescription Products

Charles Ganley, M.D., Director

Shaw Chen, M.D., Acting Deputy Director

Leah Christl, Ph.D., Associate Director for Regulatory Affairs

Division of Nonprescription Clinical Evaluation

Andrea Leonard-Segal, M.D., Director

Lesley Furlong, M.D., Clinical Team Leader

Christina Chang, M.D., M.P.H., Medical Officer

Laura Shay, Ph.D., RN, Social Science Analyst

Murewa Oguntimein, Social Science Analyst

Division of Nonprescription Regulation Development

Arlene Solbeck, IDS Reviewer

Office of Drug Evaluation III

Julie Beitz, M.D., Director

Maria Walsh, Acting Associate Director for Regulatory Affairs

Division of Reproductive and Urologic Products

Scott Monroe, M.D., Director

Lisa Soule, M.D., Clinical Team Leader

Daniel Davis, M.D., Medical Officer

Jennifer Mercier, Chief, Project Management Staff

Pamela Lucarelli, Regulatory Project Manager

Office of New Drugs

John Jenkins, M.D., Director

Pediatric and Maternal Health Staff

Lisa Mathis, M.D., Director

Office of Regulatory Policy

Jane Axelrad, J.D., Director

Office of Executive Programs, Executive Operations Staff

Vikki Kinsey, Consumer Safety Officer

FDA - Office of the Chief Counsel

Kim Dettlebach, J.D., Associate Chief Counsel

Donna Katz, J.D., Associate Chief Counsel

External Constituent Attendees:

Duramed Research, Inc.

Joseph Carrado, Vice President, Regulatory Affairs

Amy Niemann, Senior Vice President and General Manager

Michele Walsh, Director, Regulatory Affairs

Amy Hummel, Senior Associate, Regulatory Affairs

1.0 BACKGROUND:

Plan B® (levonorgestrel, 0.75 mg) is given in 2 doses, 12 hours apart, for emergency contraception. In April 2003, the applicant submitted Efficacy Supplement #011 to market Plan B® as an over-the-counter product. Duramed Research, Inc (Duramed) received approval on August 24, 2006 to market a dual-label product to allow nonprescription availability of Plan B® for women 18 years and older and by prescription only for women 17 years and younger.

On June 24, 2006, Duramed submitted a New Drug Application (NDA) to market Plan B One-Step® (levonorgestrel tablets, 1.5 mg) as a prescription-only product for women of all ages. Plan B One-Step® (levonorgestrel, 1.5 mg) is given as a single dose for emergency contraception. Duramed received an approvable letter on November 22, 2006 based on the need to submit revised labeling that meets the requirements of marketing of levonorgestrel tablets, 1.5 mg, as a prescription product for women 17 years of age and younger, and as a nonprescription product for women 18 years of age and older. On January 12, 2009, Duramed submitted a complete response to the November 22, 2006 action letter.

On April 21, 2009, FDA issued a letter to Duramed stating that it had concluded that Plan B may be made available to women 17 years of age and older without a prescription, subject to the submission and approval of revised draft labeling as a prior approval efficacy supplement to NDA 21-045 that would allow for this change in population. The letter also stated that if Duramed wanted to pursue the marketing of Plan B for women 17 years of age and older without a prescription, or other options for marketing Plan B, that a meeting was encouraged to discuss necessary labeling revisions and the content of any submission(s).

On April 28, 2009, Duramed submitted a meeting request to the FDA for an advice meeting to discuss the necessary regulatory and developmental pathway to support full over-the-counter (OTC) status for both Plan B® and Plan B One-Step®. In the meeting request, Duramed provided information and specific questions for both Plan B® and Plan B One-Step® for discussion.

1.1 MEETING OBJECTIVES:

To discuss the pathway for full OTC status for Plan B® and Plan B One-Step®.

2.0 DISCUSSION:

Preliminary responses to the questions enclosed in the April 28, 2009 meeting request were sent to Duramed via fax on May 21, 2009.

Following introductions and a brief discussion of the purpose of the meeting, the meeting agenda consisted of further discussion based on the preliminary responses from the FDA. The questions from Duramed appear below followed by the preliminary FDA responses in italics. A summary of the discussion during the meeting follows each question. For questions where no additional discussion is noted, neither Duramed nor FDA raised any additional issues pertaining to these questions at the meeting.

2.1 Plan B

1. Duramed believes that the information already submitted to the Agency in the original Rx-to-OTC supplement (S-011) submitted by Women's Capital Corporation on April 21, 2003 is sufficient to support full OTC status for Plan B, and that only revised labeling is required to be submitted. Therefore, in light of the Advice Letter of April 21, 2009, Duramed would like guidance from the Divisions as to what, if any, additional

information they envision would be required to be submitted to constitute a complete reviewable supplement to achieve full OTC status for Plan B.

FDA preliminary response:

To support a full OTC switch of Plan B without age restriction, you will need to fully address the concerns regarding nonprescription use of Plan B by women 16 years of age and younger that were articulated in Dr. Steven Galson's memorandum dated August 26, 2005, and our May 6, 2004 letter. We suggest you address these concerns by presenting any data that are available, including data from the literature, that would support OTC status for Plan B for women 16 years of age and younger. We will review these data and determine whether they are adequate to address the concerns.

You should also provide a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should encompass the time from the last approval date through the time of submission. The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

In addition, you should provide a summary of worldwide OTC experience on the safety of this drug (including both one- and two-dose regimens) in this population for emergency contraception, including an updated estimate of use of this drug marketed in other countries.

You will also need to submit proposed labeling revised to address OTC access with no age restriction. We refer you to our response to Question 3 for further details regarding the submission of any supplement.

Additional discussion for Question 1:

Duramed stated that they felt that the data previously submitted to NDA 21-045/S-011 adequately supported approval of Plan B ® as an OTC product for women of all ages. Duramed sought clarification on why it was necessary to again address the issues raised in Dr. Steven Galson's memorandum dated August 26, 2005.

FDA explained that the approval of the Plan B ® product approximately three years ago was based on CDER's conclusion regarding the age restriction. In this case, as for any approved application, the concerns articulated in the decision of record at the time of approval need to be addressed in order to make a change post-approval to the approved labeled population. FDA further explained that the support for changing the labeled population could come from new data, literature, cogent arguments addressing CDER's position at the time of approval, or other information.

FDA stated that it would be logical that any rationale to support a change in the labeled population for Plan B ® to an OTC product for women of all ages would also apply to the Plan B One-Step ® product.

2. Duramed asserts that S-011, which contained reports of the Plan B Actual Use Study and Plan B Label Comprehension Study, included a sufficient number of pediatric subjects to qualify for Pediatric Exclusivity under Section 505(A) of the Federal Food, Drug and Cosmetic Act. Do the Divisions concur?

FDA preliminary response:

Your application does not qualify for pediatric exclusivity. To obtain pediatric exclusivity, a Written Request for studies must be issued by the Agency and you must submit studies that fairly respond to the Agency's Written Request. The studies which qualify an applicant for pediatric exclusivity must be submitted after the Written Request has been issued. Please see Guidance for Industry, "Qualifying for Pediatric Exclusivity under Section 505A of the Federal Food, Drug, and Cosmetic Act." The Agency has not issued a Written Request for studies with Plan B, and the study to which you refer has already been completed and the results submitted to the agency.

In addition, the Best Pharmaceuticals for Children Act, which was reauthorized as Title V of the Food and Drug Administration Amendments Act of 2007 (FDAAA), now requires that for pediatric exclusivity to attach to a product, that product must have 9 months of existing patent and/or exclusivity at the time that the pediatric exclusivity determination is made. The exclusivity determination is now made 180 days after submission of the full study reports. This means that, to be eligible for pediatric exclusivity, final studies must be submitted 15 months prior to expiration of patent and/or other marketing exclusivity. Since there are no active patents for the NDA, and exclusivity expires August 24, 2009, this application could not qualify for pediatric exclusivity, even if FDA were to consider issuing a Written Request, unless new patents or new marketing exclusivity were obtained to which pediatric exclusivity could attach.

The Orange Book lists no active patents and the following exclusivity for NDA 21045:

<i>Appl No</i>	<i>Prod No</i>	<i>Exclusivity Code</i>	<i>Exclusivity Expiration</i>
021045	002	NP	Aug 24, 2009

Additional discussion for Question 2:

Duramed asked whether there were any circumstances that would allow Duramed to receive pediatric exclusivity for Plan B ®.

FDA explained that there is no exception in the statute and that the preliminary comments outline why the Plan B ® product would not be eligible for pediatric exclusivity.

FDA explained that it may be possible for pediatric exclusivity to be granted for the Plan B One-Step ® product based on the ongoing actual use study for Plan B One-Step ®. FDA stated that Duramed could submit a request for the agency to issue a Written Request for studies with Plan B One-Step ®.

3. What is the Division's perceived timing around this review and approval of the OTC amendment?

FDA preliminary response:

Your proposal as outlined in your April 28, 2009, meeting request involves expansion of the patient population (adolescents aged 17 years and younger) for the OTC indication; therefore, the submission of an efficacy supplement would be required.

If you intend to propose an OTC switch for adolescents 17 years of age only, as outlined in our April 21, 2009, letter, you would need to submit an efficacy supplement to NDA 21-045. No additional data would be required to be submitted in this supplement. You would only need to submit revised labeling to address the change in age for OTC access.

However, if you intend to pursue an OTC switch for adolescents 17 years and younger, you would need to submit an efficacy supplement containing the information and/or data to address the concerns regarding nonprescription use of Plan B by women 16 years of age and younger outlined in our response to Question 1.

The PDUFA review timeline of 10 months would apply to either efficacy supplement. However, we will review your submission(s) in as timely a manner as possible.

Additional discussion for Question 3:

FDA clarified for Duramed that although labeling alone would need to be submitted in a supplement to change the age to 17 years of age for OTC access, the type of supplement would be an efficacy supplement, not a labeling supplement.

Upon further discussion, it was agreed that a safety update should be submitted to NDA 21-045 encompassing the time since the approval of NDA 21-045/S-011, regardless of the change in labeled population that Duramed chose to pursue for either NDA 21-045 or NDA 21-998.

FDA stated that if Duramed submitted a supplement for NDA 21-045 proposing an OTC switch for adolescents 17 years of age only, the submission would be subject to a 10-month review clock, but the review would be conducted as expeditiously as possible and would likely take less than 10 months.

2.2 Plan B One-Step

4. For the original Plan B One-Step NDA submitted January 24, 2006, Duramed believes that, pursuant to 21 CFR 314.108 (b)(4) and a positive action, an exclusivity period of 3 years from the date of approval of the application will be granted. Do the Divisions confirm that this exclusivity would be granted?

FDA preliminary response:

It is premature to comment on the eligibility for 3-year exclusivity at this time. Three-year exclusivity is granted upon approval of a new drug application when new clinical

studies, essential for approval, have been conducted or sponsored by the applicant. Whether specific clinical data used to support the application are essential to the approval of the NDA is a review issue. FDA does not award or grant exclusivity prior to approval of a drug product. The Office of Generic Drugs will determine whether the application has qualified for 3-year exclusivity at the time of approval of Plan B One-Step.

5. This product is currently under review with a PDUFA goal date of July 10, 2009, based on Duramed's Complete Response to the Approvable Letter of November 22, 2006. In the Approvable Letter, the Division stated that the Plan B One-Step label should directly mirror the label of the Plan B product. Duramed believes that conversion of the Plan B One-Step labeling to full OTC status can be handled through during the labeling negotiation process, (which as of the date of this meeting request has not yet begun for this product) with no extension of the PDUFA date. Do the Divisions concur?

FDA preliminary response:

If you intend to amend the label to provide full OTC status without age restriction, we would consider this a major amendment, which would extend the PDUFA goal date up to three months. The amendment should include, based on data and information regarding the sameness/differences between Plan B and Plan B One-Step, the same or similar data and/or other information described in our response to Question 1, as well as any additional data and/or information that are specific to the Plan B One-Step product. The amendment should also include a safety update as described above.

Additional Administrative Comments:

Comments shared with you today are based upon the contents of the meeting request, which is considered to be an informational aid to facilitate the meeting discussion. Review of the information submitted to the NDA might identify additional comments or informational requests.

For applications submitted after February 2, 1999, applicants are required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

General Additional Discussion:

FDA asked Duramed to provide an overview of their plans at this time regarding making changes to the labeled OTC population and an update on the ongoing studies for Plan B One-Step ®.

Duramed explained that they were recently purchased by Teva and that any plans would be dependent on the decisions of the new management. Duramed stated that they were fairly certain that any decision regarding changes to the labeled population beyond an OTC switch for women

17 years of age would occur after the July 12, 2009 PDUFA goal date for NDA 21-998, Plan B One-Step ®.

Duramed stated that the label comprehension study for Plan B One-Step ® was completed and published by the investigators. Duramed provided the packaging and labeling for the study, but did not sponsor the study. Therefore, Duramed does not have access to the raw data.

The actual use study is still ongoing, but there have been some issues with enrollment and informed consent because the Plan B One-Step ® product is still an investigational drug. Duramed stated that they were hopeful that the study would proceed in a better fashion once Plan B One-Step ® was approved for marketing in the United States under NDA 21-998.

3.0 SUMMARY OF KEY DISCUSSION POINTS AND ACTION ITEMS:

1. Duramed will submit revised labeling as an efficacy supplement to NDA 21-045 Plan B ® to propose the OTC switch for adolescents 17 years of age.
2. Duramed will amend NDA 21-998 Plan B One-Step ® with the submission of revised labeling to change the age for OTC access to 17 years of age.
3. Duramed will submit a safety update to both the proposed efficacy supplement for NDA 21-045 and to the pending application NDA 21-998 when the revised labeling is submitted.
4. If Duramed chooses to pursue full OTC approval of Plan B ® and Plan B One-Step ®, without age restriction, Duramed will address the concerns articulated at the time of the approval of NDA 21-045 S-011 for Plan B ®.
5. Duramed will evaluate the continuation of the actual use study for Plan B One-Step ® following discussion with upper management in Teva.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Neither FDA nor Duramed identified any issues requiring further discussion at this time.

5.0 ATTACHMENTS AND HANDOUTS

There were no handouts or slides used at this meeting.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Andrea Segal
6/26/2009 12:50:11 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 45,796

Duramed Research, Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph.
Vice President, Clinical Regulatory Affairs
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for levonorgestrel 1.5 mg tablet.

We also refer to the meeting between representatives of your firm and the FDA on May 22, 2007. The purpose of the meeting was to discuss the design and conduct of the planned levonorgestrel 1.5 mg tablet Actual Use and Label Comprehension studies.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Cassandra Sherrod, R.Ph., Regulatory Project Manager, at (301) 796-0997.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Acting Director
Division of Reproductive and
Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, M.D.
Director
Division of Nonprescription
Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 22, 2007
TIME: 2:00 p.m. - 3:30 p.m.
LOCATION: White Oak Conference Bldg. 22, Rm. 1313
APPLICATION: IND 45,796
DRUG NAME: levonorgestrel tablets, 1.5 mg
TYPE OF MEETING: B
MEETING CHAIR: Andrea Leonard-Segal, M.D., Director, Division of Nonprescription Clinical Evaluation (DNCE)
MEETING RECORDER: Kassandra Sherrod, R.Ph., Regulatory Project Manager, Division of Reproductive and Urologic Products (DRUP)

FDA ATTENDEES

Sandra Kweder, M.D., Deputy Director, Office of New Drugs
Charles J. Ganley, M.D., Director, Office of Nonprescription Products
Andrea Leonard-Segal, M.D., Director, DNCE
Joel Schiffenbauer, M.D., Deputy Director, DNCE
Bindi Nikhar, M.D., Medical Team Leader, DNCE
Joseph Porres, M.D., Medical Reviewer, DNCE
Laura Shay, C.R.N.P., M.S., Social Science Analyst, DNCE
Leah Christl, Ph.D., Chief, Project Management Staff, DNCE
Helen Cothran, Interdisciplinary Scientist Team Leader, Division of Nonprescription Regulation Development (DNRD)
Arlene Solbeck, Interdisciplinary Scientist Reviewer, DNRD
Stan Lin, Ph.D., Associate Director, Division of Biometric IV, Office of Biostatistics
Robert Nelson, M.D., Ph.D., Pediatric Ethicist, Office of Pediatric Therapeutics, Office of Commissioner
Julie Beitz, M.D., Director, Office of Drug Evaluation III
Scott Monroe, M.D., Acting Division Director, DRUP
Lisa Soule, M.D., Clinical Team Leader, DRUP
Daniel Davis, M.D., Medical Officer, DRUP
Jennifer Mercier, Chief, Project Management Staff, DRUP
Kassandra Sherrod, R.Ph., Regulatory Project Manager, DRUP

DURAMED ATTENDEES

Joseph A. Carrado, M.S., R.Ph., Vice President, Clinical Regulatory Affairs and Quality Assurance
Fred Wilkinson, President and COO, Duramed Pharmaceuticals
Nancy Ricciotti, MSN, Director, Clinical Operations
Wendy Faries, Clinical Associate, Clinical Regulatory Affairs
Howard Hait, Vice President, Biostatistics and Data Management
Diane Harrison, M.D., MPH, Sr. Director, Clinical Operations
Wayne Mulcahy, Ph.D., Vice President, Clinical Operations
Michele Walsh, Associate Director, Clinical Regulatory Affairs
Tina Raine-Bennett, MD, MPH, Consultant, Associate Professor, Obstetrics, Gynecology, and Reproductive Sciences-UCSF

BACKGROUND

Plan B® (0.75 mg levonorgestrel x 2 tablets) was approved by the Agency on July 28, 1999. Women's Capital Corporation submitted a prescription (Rx)-to-over-the-counter (OTC) switch supplement on April 11, 2003. The supplement was ultimately approved on August 24, 2006 for OTC sale to consumers 18 years of age and older and for Rx sale for women under the age of 18 years.

On January 24, 2006, Duramed submitted a new drug application (NDA) for Levonorgestrel tablets, 1.5 mg, an emergency contraceptive pill regimen consisting of a single dose of 1.5 mg levonorgestrel to be taken within 72 hours of unprotected sexual intercourse. The application received an approvable action pending submission of revised labeling necessary to market Levonorgestrel 1.5 OTC for women aged 18 years and above, and as a prescription product for women younger than 18 years. The sponsor is seeking guidance on the consumer behavior and comprehension studies needed to support the distribution of levonorgestrel 1.5 mg tablet as an OTC product without an age restriction.

MEETING OBJECTIVES

To discuss the design and conduct of the planned Levonorgestrel 1.5 mg tablet Actual Use and Label Comprehension studies to support a new drug application to make available the levonorgestrel 1.5 mg tablet OTC without an age requirement.

DISCUSSION

Preliminary responses to the questions enclosed in the April 19, 2007 meeting package were sent to Duramed via e-mail on May 21, 2007. The questions from Duramed appear below followed by the preliminary FDA responses in italics. Following introductions and a brief discussion of the purpose of the meeting, the meeting agenda consisted of further discussion based on the preliminary responses from the FDA. A summary of the discussion during the meeting follows each question. For questions where no additional discussion is provided, neither Duramed nor FDA raised any additional issues pertaining to these questions.

Administrative

1. *Duramed acknowledges that the primary decision maker for the Plan B® (levonorgestrel 0.75mg tablet) OTC product with the Rx requirement for women age 17 and younger was the Office of the Center Director (Dr. Steven Galson) and not the Division of Reproductive and Urologic Products nor the Office of Nonprescription Products. Therefore, can assurances be provided:*
 - a. *That the primary decision maker, Dr. Steven Galson, Center Director, has agreed upon all guidance, comments and advice that will be given to Duramed?*

FDA Preliminary Response

Dr. Galson has been appropriately briefed and concurs with the responses we are providing to your questions.

- b. *That the primary decision maker, Dr. Steven Galson, Center Director, is in agreement with the proposed Label Comprehension and Actual Use studies proposed to remove the Rx requirement for women age 17 and under?*

FDA Preliminary Response

There are ways to improve the proposed Label Comprehension and Actual Use studies for levonorgestrel 1.5 mg tablets so they provide the data that is necessary to determine whether levonorgestrel 1.5 is appropriate for OTC use by adolescents. Your proposed sample size for both studies is unacceptable for adolescents of certain ages (see FDA Responses for Questions 3 and 4). In addition, we have design recommendations related to testing the adolescent population (see FDA Responses for Questions 3-9).

You will also need to address how you plan to obtain informed consent from minors enrolled in the actual use study. We acknowledge your explanation about minors being able to consent for contraceptive services in various states without parental consent; however, this study is being conducted under an IND for an unapproved drug product.

- c. *That any requirements can be provided in a timely manner if there exists internal disagreement on the range and scope of the studies required to remove the current prescription requirement?*

FDA Preliminary Response

Refer to FDA Response for Question 1a.

2. *The current Plan B[®] (levonorgestrel 0.75 mg tablet) IND 45,796, will be amended to include CMC information on the levonorgestrel 1.5 mg tablet instead of opening a new, separate IND to conduct the Actual Use and Label Comprehension studies. Does the Division agree with this plan?*

FDA Preliminary Response

This approach is acceptable.

Label Comprehension Study

3. *Does the Division agree that the following 6 Communication Objectives are adequate to evaluate the successful comprehension of the Plan B 1.5 label for OTC use?*
- *Plan B[®] 1.5 is indicated for prevention of pregnancy after unprotected sex.*
 - *Plan B[®] 1.5 should not be used for regular contraception.*
 - *Plan B[®] 1.5 should be taken as soon as possible after unprotected sex.*
 - *Plan B[®] 1.5 should be taken within 72 hours after unprotected sex.*
 - *Plan B[®] 1.5 does not prevent sexually transmitted diseases or HIV/AIDS.*
 - *Plan B[®] 1.5 should not be used by women who are already pregnant.*

FDA Preliminary Response

Yes, we agree that these are the important communication objectives on the outer package. However each objective is not of equal value in terms of safe and effective use of the product. We suggest that the communication objectives be divided into the following primary and secondary objectives based on their importance to the understanding of safe and effective product use with a corresponding target level of comprehension for each objective:

1. *Primary Communication Objectives: Based on results from the previous label comprehension study, the target level of comprehension for the primary objectives should be $\geq 80\%$ with 95% statistical confidence.*
 - *Levonorgestrel 1.5 is indicated for prevention of pregnancy after unprotected sex.*
 - *Levonorgestrel 1.5 should be taken as soon as possible after unprotected sex.*
 - *Levonorgestrel 1.5 does not prevent sexually transmitted diseases or HIV/AIDS.*
2. *Secondary Communication Objectives: The target level of comprehension for each of the secondary objectives should be $\geq 70\%$ with 95% statistical confidence.*
 - *Levonorgestrel 1.5 should be taken within 72 hours after unprotected sex.*
 - *Levonorgestrel 1.5 should not be used for regular contraception.*
 - *Levonorgestrel 1.5 should not be used by women who are already pregnant.*

We also refer you to FDA Response for Question 6.

Your proposed total sample size of 350 subjects who are 12-17 years old may be adequate; however your proposed sample size for the 12, 13, and 14 year olds is unacceptable. You need to adequately enrich the sample size for the younger ages (12, 13, 14, and 15 year olds) with a minimum of 50 subjects for each age in order to provide enough data for a meaningful analysis. In addition, because 11 year olds may be eligible to use this product, this age group should also be tested with a minimum sample size of 50. Therefore you should have a minimum sample size of 50 subjects for each age (11-17 years old). The total sample size should be based on the target level of comprehension for the communication objectives described above.

Discussion at the Meeting

The sponsor expressed concern about the number of subjects needed in the younger age groups. Based upon the information they have, subjects in those younger ages will be difficult to recruit. The sponsor indicated that the sites that they are using do not have a high number of patients who are younger than 15 years of age. For the 11 year olds, the sponsor has looked at the data and determined that only 10-30% of all 11 year olds have reached menarche. Of that 30%, only a very small percent is sexually active.

The Agency referred the sponsor to the memo from Dr. Steven Galson regarding the Plan B (levonorgestrel) OTC approval. Use of emergency contraception in this younger group is a concern and could remain a concern for this product if the sponsor does not provide adequate information as to why these younger ages cannot be included or why the actual number of subjects studied will be lower than the number requested by the FDA.

FDA Preliminary Response

The REALM-Teen score is broken down into education levels. Given that the eligibility criteria for low literacy for your proposed study is less than or equal to 7th grade, you should provide a breakdown of the REALM-Teen scores for all the participants tested in order to ensure that participants with different levels of low literacy are tested.

You have proposed a two group design comparing comprehension of the package label between females age 12-17 years to females age 18-19 years. You describe that because Plan B OTC is approved OTC for 18-19 year olds, the 18-19 year old women in the study will provide a 'benchmark' for the level of comprehension that is considered adequate. As described above, the 'benchmark' for the primary and secondary communication objectives is 80% and 70% respectively. Having this comparison group is important only in that it will allow us to assess the sensitivity of the study questions.

You describe that "a participant will be considered to have understood a concept if she correctly answered at least 60% of the questions specifically developed to assess that concept". Given that one of the communication objectives is being tested using only two questions it is unclear how this analysis can be achieved. In addition, based on categorizing the communication objectives into primary and secondary objectives as described above, you may need to reconsider the number of questions you are using to test for each objective and submit a new proposal for the percentage of correct answers that you will consider correct for each of the objectives.

In your analysis, you will need to look for age related trends. In addition, we remind you that you will need to describe all variables you will be analyzing and how they will be analyzed in a detailed statistical plan a priori.

The way you pose questions in your survey questionnaire should not introduce bias into the study results. The levonorgestrel 1.5 Survey Questionnaire that you propose to use in your label comprehension study contains primarily questions with simple yes/no or correct/incorrect response choices. A simple yes/no or correct/incorrect response choice allows a subject to choose a correct answer 50% of the time by chance alone. This is inadequate. Probing for the reasons why subjects answer a question the way they do needs to be conducted and responses need to be recorded verbatim for all questions that allow for a yes/no or correct/incorrect response. Understanding why subjects answer questions the way they do allows for richer analysis of the data. If subjects test low on a communication objective, and there is no qualitative data to understand why, interpretation of the result is difficult and there is no information upon which to base label improvement. In addition, if a subject chooses the correct answer to a yes/no question but the reason they provide for choosing that answer demonstrates an obvious lack of understanding, the yes/no answer would be considered incorrect.

Because the reasons why subjects answered questions the way they did were not collected in the label comprehension study for Plan B 0.75, it is unclear why only 67% of the subjects understood that Plan B should not be used for regular contraception. We recommend that you re-evaluate the language used to convey this message and test new language that may be better understood (e.g., levonorgestrel 1.5 should not be used in place of regular birth control).

Additional recommendations for the levonorgestrel 1.5 Survey Questionnaire include the following:

- For Questions 11, 12, and 13 you should provide the subject with additional response choices such as 2=sometimes, and 3=I don't know. Otherwise the subject has a 50% chance of being correct by chance alone.*
- All responses to the scenario based questions (14-25) should be followed up with a probing question asking the subject why or why not. Verbatim answers to these probing questions should be recorded and submitted for analysis.*

- *Question 28 should be asked as an open-ended question such as [REDACTED] (b) (4)*
- *Because the concept of 'regular birth control' was poorly understood in the label comprehension study for Plan B 0.75 mg, we recommend that you develop an open-ended question that asks subjects to define the term 'regular birth control'. We also recommend that you perform a similar assessment for the term 'unprotected sex'.*
- *In your label comprehension study for Plan B 0.75 mg, the sample size after categorizing participants according to their responses to the Confidential Questionnaire was too small to allow for any meaningful interpretation. It is unclear how answers to the Confidential Questionnaire for this study will provide any new insight into the results of this label comprehension study.*
- *In addition to literacy level, prior EC use, history of birth control use as well as a history of being sexually active may potentially impact the ability to comprehend the levonorgestrel 1.5 label. Therefore these demographic data elements should be collected on all subjects.*
- *Because a subject who received sex education may have a better understanding about sexuality and reproductive health, an open-ended question should also be asked to assess whether or not a subject received sex education and, if so, where (e.g. school, home etc.) and by whom (e.g., older sibling, friend, parent, teacher etc.).*
- *Be sure that your survey questionnaire addresses all of the communication objectives (see FDA Response to Question 6).*
- *It is unclear why you are planning to shuffle the question order for successive subjects to minimize the effects of response bias. All subjects should receive the questions in the same order to eliminate change in order as a potential confounding variable. The survey should be written so that it will not bias the subjects. This includes a proper order to the questions so that one question does not educate the subject in answering subsequent questions.*

Discussion at the Meeting

Duramed expressed concern about evaluating verbatim responses to questions in the Label Comprehension study, particularly if a correct answer might be negated by the subject's verbatim response if it suggested that she had provided the correct answer for incorrect reasons. FDA noted that yes/no options allow a 50% chance of getting the correct answer regardless of the subject's understanding, and only examination of the verbatim responses will allow evaluation of understanding. Duramed stated that they will consider adding to the questionnaire some items where verbatim responses are recorded, but they request that evaluation of these more detailed responses be used only to guide improvements in the label, and not be allowed to decrease the percent of subjects achieving correct responses. Duramed also expressed concern that collecting verbatim responses would prolong the testing to the point of subject fatigue. This could impact the study results. FDA stated that they will hold further internal discussions about the need to collect the verbatim responses and the way in which these responses would be used.

4. Does the Division agree with the proposed sample size of 350 participants age 12-17 years and 350 participants age 18-19 years as calculated by a 60% rate that study subjects demonstrated understanding of all communication objectives? (See Attachment 1, page 12 of 18).

FDA Preliminary Response

The total sample size should be based on the target level of comprehension for the communication objectives described above (see FDA Response to Question 3). We believe that there should be equal distribution of subjects for each age group. We refer you to FDA Response to Question 3 for more discussion of the performance standards for comprehension of the primary and secondary communication objectives.

Discussion at the Meeting

Duramed stated that they have decided to eliminate the 18-19 year old comparison group.

- 5. Does the Division agree with the potential to over enroll in the 12-14 years age group in the Label Comprehension study, as participation of this age group in the Actual Use study may be low, reflecting the population of teenagers who seek emergency contraception? (See Attachment 1, page 9 of 18).**

FDA Preliminary Response

As stated in the FDA Response to Question 3, the number of subjects age 12, 13, and 14 that you propose to test in the label comprehension study needs to be larger in order to provide meaningful data for analysis, and you also need to test 11 year olds. You will also need to add 11 year olds to your sample and enrich the sample size of the younger age groups for your Actual Use Study (see FDA Response to Question 9).

Discussion at the Meeting

Duramed expressed concern about the FDA requiring the enrollment of 11 year olds in the Label Comprehension and Actual Use studies. Duramed stated that they felt it would be difficult to enroll this population based on the expected low percentage of eligible subjects and the fact that this population does not present at the clinics. Duramed stated that they would enroll 11 year old girls in the studies if they presented, but that actively seeking that population to enroll and having set enrollment numbers would be problematic. Duramed indicated that the sites that they are using do not have a high number of patients who are younger than 15 years of age. For the 11 year olds, Duramed has looked at the data and has determined that only 10-30% of all 11 year olds have reached menarche. Of that 30%, only a very small percent is sexually active. FDA recommended that Duramed submit their explanation, with supporting data where possible, in writing to the FDA for review and comment. FDA stated that use of emergency contraception in this younger group is a concern. FDA strongly recommended that Duramed review the memo from Dr. Galson, dated May 6, 2004 regarding the Plan B (levonorgestrel) OTC approval, including the reference "14 and Younger: The Sexual Behavior of Young Adolescents," The National Campaign to Prevent Teen Pregnancy, May 2003" cited in the memo, before providing their submission to FDA.

Duramed questioned what FDA meant by "provide meaningful data for analysis" as stated in the Preliminary Response to Question 5. FDA stated that the numbers of subject in the younger age groups (12, 13 and 14 year olds) was not adequate and that Duramed needed to enroll a greater number of subjects of those ages. FDA explained that the older age groups cannot drive the overall comprehension rate to over 80% and that there needs to be adequate sampling to ensure that the younger age groups are adequately represented.

6. *Does the Division agree with Duramed's plan to evaluate the comprehension of the outer carton (box) as this simulates a real OTC setting and not to evaluate the inner carton and consumer information leaflet for the Label Comprehension study?*

FDA Preliminary Response

No, you should also test comprehension of key communication objectives in the consumer leaflet as was done in the previous label comprehension study, for example, information regarding severe abdominal pain (ectopic pregnancy) and seeking medical help when this occurs.

Because these communication objectives are not necessary for an appropriate self-selection decision at point-of-purchase, they can be considered secondary communication objectives with an a priori targeted level of comprehension of $\geq 70\%$.

Discussion at the Meeting

Duramed noted that the consumer information leaflet (CIL) was not tested for comprehension in the previous label comprehension study and questioned why FDA was requesting that it be tested now, especially since this will introduce inconsistency with the prior study. FDA explained that there are certain concepts in the CIL that were tested in the last label comprehension study such as abdominal pain/ectopic pregnancy. FDA added that Dr. Galson had stated that he wanted consistency between what was tested in the previous study and what is proposed in the current study. FDA explained that only specific key concepts should be tested, not the entire CIL. FDA agreed to discuss this issue further internally and provide additional guidance to Duramed as a post-meeting addendum to the meeting minutes.

7. *Does the Division agree with Duramed's proposed label for use in the Label Comprehension and Actual Use studies (see Attachment 5)?*

FDA Preliminary Response

Yes we agree. However, we have the following comments and recommendations:

Principal Display Panel

1. You may want to enhance the information in the first bullet to read: "**Reduces the chance of pregnancy after unprotected sex** (such as: if your regular birth control method failed or was not used correctly, or after sex without birth control)." or "**For emergency use to reduce the chance of pregnancy after unprotected sex** (such as if your regular birth control failed or was not used correctly, or after sex without birth control)."
2. Consider rewording the first sentence in second bullet to read: "**Do not use in place of regular birth control.**" Bold both sentences in the second bullet. It is not necessary to use capital letters for each word in the second sentence of the second bullet if it is bolded.
3. Consider rewording the third bullet to read" "**Does not protect against HIV/AIDS or other STDs**
4. To be consistent in the use of periods, use them at the end of all the bullets or don't use them at all.

5. The bolded text for extra emphasis under "Take Plan B 1.5:" in the upper right of the carton is acceptable.

Drug Facts

1. Right align the subtitle "Purpose".
2. Under "Use," reword the statement to read: "reduces the chance of pregnancy after unprotected sex (such as if your regular birth control method failed or was not used correctly, or after sex without birth control)".
3. Under "Sexually transmitted diseases (STDs) alert:" bold the word "not" in the first sentence.
4. Under "Sexually transmitted diseases (STDs) alert:" we note that you have added a statement about condom usage that was originally in the "Other information" section for Plan B (0.75 mg). Although condom usage information is not necessary for the safe and effective use of this product, we believe that it is important information that might not be read otherwise and that even might help prevent the consumer from having to use levonorgestrel 1.5 again if it is read (i.e., if a consumer remembers to use a condom to prevent STDs, they will also not be having unprotected sex). Therefore, we believe it is acceptable to locate this information in the "Sexually transmitted diseases (STDs) alert" rather than farther back in the Drug Facts label.
5. Under "Directions," revise the first statement, "Take Plan B 1.5", to include the target population and to delete the brand name (brand names are not allowed in the Drug Facts label).
6. Under "Directions," delete the period at the end of the second bulleted statement.
7. Under "Other information," we note that (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]. This is acceptable.
8. Under "Other information," delete the fourth bullet about (b) (4) This information is already covered in the (b) (4)
The second statement about (b) (4) and should also be deleted.
9. Under "Other information," add a statement to inform the consumer about the tamper-evident feature of the package (in accordance with 21 CFR 211.132) such as "do not use if carton is opened or if blister unit is broken".
10. Under "Questions or comments?," bold the telephone number (in accordance with 21 CFR 201.66(c)(9)). Add the proper phone number and website.

Consumer Information Leaflet

1. Revise the Consumer Information Leaflet in accordance with the above comments.

Actual Use Study

8. **Does the Division concur with the current study design of the Actual Use Clinical Trial (DR-LEV-302) including but not limited to study objectives, patient population, assessments of correct and repeat product use, assessment of safety and sample size? (See Attachment 7)**

FDA Preliminary Response

Overall the design of your actual use study is similar to the design of your previous actual use study and is acceptable. However we have the following recommendations based on issues specific to testing the adolescent population that we strongly encourage you to consider:

The self-selection procedure you proposed is not acceptable. The Actual Use study should not exclude a subject with a known contraindication to EC that was documented by the clinic staff at a previous visit or a subject who voluntarily reveals that she suspects or thinks she is pregnant. In order to simulate the OTC environment, participation in the study should be open to all females < 18 years old who come to the clinic requesting EC. The only exclusion criteria should be:

- \geq age 18
- Inability to speak and understand English

Once the levonorgestrel 1.5 outer package has been read and the subject makes a self-selection decision to either use the product or not use the product, verbatim responses to a follow-up question asking the subject why they chose to use the product or why they did not choose to use the product should be collected on all subjects. The medical history, including medication allergies and pregnancy status should then be collected in order to assess for appropriate self-selection. All of this data can be collected after a confidentiality agreement is signed. Subjects who incorrectly self-selected can be withheld from the use portion of the study. All other subjects would then be asked to sign the consent form and continue to the use portion of the study.

In your January 30, 2007 Actual Use Protocol Synopsis you state that the following questions will be asked to assess whether or not the subject used the product appropriately:

Did you use levonorgestrel 1.5 according to all the directions on the box?

- If no, what instructions did you not follow?
- Did you know you were not following the instructions when you took the levonorgestrel 1.5 tablet or did you realize that only after you took it?

These are leading questions and should not be used. Appropriate use of the product should be assessed through open-ended questions such as "when did you take the product and why did you take the product?" with additional probing questions such as "when did you have sex?" It is important that all verbatim responses be recorded and the way a question is asked and the order in which a question is asked does not create bias. For example, asking when the subject had sex should not be the first question asked because it may bias the subject to provide an answer to the drug timing question that is correct based on the label but not the way they actually took the drug. We recommend that you submit a copy of your proposed recruitment materials and study coordinator script for review and comment. All of these, if not properly written, can bias the study results.

Subjects who return to the clinic for additional doses of levonorgestrel 1.5 over a six month period should not be re-enrolled as a new subject. Repeat use data needs to be captured on

these subjects separately and should include the reason(s) for needing the product, if they received Plan B at other clinics since enrollment, pregnancy status, and any data that is generated from the 1, 4, and 8 week follow-up contacts.

The previous study had poor adherence rate to follow-up visits in the younger age group. There was also a poor rate of return of the diary cards for all age groups. Therefore we recommend that you develop creative ways to capture follow-up data without biasing the study such as providing monetary incentive for each follow-up visit. If there is a heavy reliance on telephone contact due to transportation issues, you may need to be sure that all subjects have access to a cell phone in order to facilitate adherence to follow-up contacts and to insure privacy.

We note that the informed consent for the Actual Use Study does not provide an adequate explanation that levonorgestrel 1.5 is a new formulation that has not yet been approved by the FDA. In addition, all medical risks listed on the product package should be listed in the informed consent.

- 9. The study will enroll approximately 300 subjects to achieve a minimum of 200 subjects who each use the study product at least once. Does the Division agree with Duramed's plan to allow enrollment in the Actual Use Study to represent the population of teenagers seeking emergency contraception, rather than set a priori quotas for enrollment based on age?**

FDA Preliminary Response

No, you should set an a priori quota for enrollment based on age in order to provide data for a meaningful analysis. The primary objective for your actual use study is to determine the frequency of contraindicated and incorrect use of levonorgestrel 1.5 in a simulated OTC condition. Therefore you have two primary endpoints: percentage of subjects who correctly self-select and percentage of subjects who correctly use the product. In your previous study, 95% of the subjects ≤ 16 year reported correct use for taking the first pill within 72 hours. Your proposed sample size of 200 is adequate to show an overall true correct use rate is not lower than 80-95% if the point estimate of that rate is 85% or higher. However you will need to enroll a minimum of 25 subjects for each of the younger ages (11, 12, 13, and 14 year olds) in order to show that the correct use rate is not less than 78% with confidence, among these age groups combined, again assuming that the point estimate of the correct use rate is 85% or higher for adolescents of these ages. In your analysis you will need to look for age related trends, therefore you will also need to have an evenly distributed number of subjects who are age 15, 16 and 17.

Discussion at the Meeting

Duramed expressed concern regarding the FDA's request for a minimum sample size requirement for 12-year-old subjects in the Actual Use study. Duramed explained that use of the product by adolescents this age may not support the enrollment requirement. Duramed stated that the study is designed with "all-comers" enrollment, as was the previous Actual Use study, and that the numbers from the first study mirror the census numbers. FDA stated that they recognized the possible difficulties with enrollment of 12 year olds and recommended that Duramed submit their position regarding this, with data to support their position, to the FDA for review and comment. FDA recommended that Duramed include information on the actual numbers of 11, 12, 13, and 14 year olds that seek care and emergency contraception at clinics.

Additional FDA Administrative Comments

Comments shared with you today are based upon the contents of the meeting package, which is considered to be an informational aid to facilitate the meeting discussion. Review of the information submitted to the IND or NDA might identify additional comments or informational requests.

We encourage you to submit study protocols for FDA review and comment prior to initiating any studies. We remind you of the Guidance for Industry Special Protocol Assessment, which can be found at <http://www.fda.gov/cder/guidance/3764fnl.pdf>.

For applications submitted after February 2, 1999, an applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

DECISIONS (AGREEMENTS) REACHED

- Duramed will not include 18 and 19 year olds in the Label Comprehension study.
- Duramed will provide a full update on the CARE program from the Plan B (levonorgestrel) Tablets OTC by the end of July 2007. Duramed indicated that they have conducted one meeting with the pharmacy groups to discuss educational programs and have completed their first point of purchase program. Through this program they are learning that many stores (pharmacies) do not dispense Plan B and that the number of these stores far exceeds the number that are in violation of the age checking requirement.

ACTION ITEMS

- Duramed will submit information supporting their contention that enrollment of 11 year olds in both the Label Comprehension and Actual Use studies is not feasible because females in this age group generally do not present for emergency contraception.
- Duramed will submit information about the feasibility of enrolling a set number of 12 year olds in the Actual Use Study.
- Duramed will consider including open-ended probing questions in the Label Comprehension Study to capture verbatim responses and will submit a revised study protocol for FDA review and comment.
- FDA will comment further on the need to collect verbatim responses from the open-ended probing questions and how the information would be used.
- FDA will comment on the need to test the CIL for comprehension of key communication objectives.

POST-MEETING ADDENDUM

- Following internal discussion, FDA has concluded that there is no need for Duramed to conduct a consumer comprehension study with the consumer information leaflet (CIL) or any parts of the CIL.
- FDA has determined that they will not provide general comments at this time on the need to collect verbatim responses from follow-up probe questions in the Label Comprehension study. Instead, the FDA will provide comments on Duramed's revised Label Comprehension study protocol that Duramed intends to submit because the protocol will be revised based on the discussion at the meeting.

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this page is the manifestation of the electronic signature.**

/s/

Andrea Segal
6/14/2007 04:58:07 PM

Scott Monroe
6/14/2007 05:11:47 PM